The American Journal of Medicine



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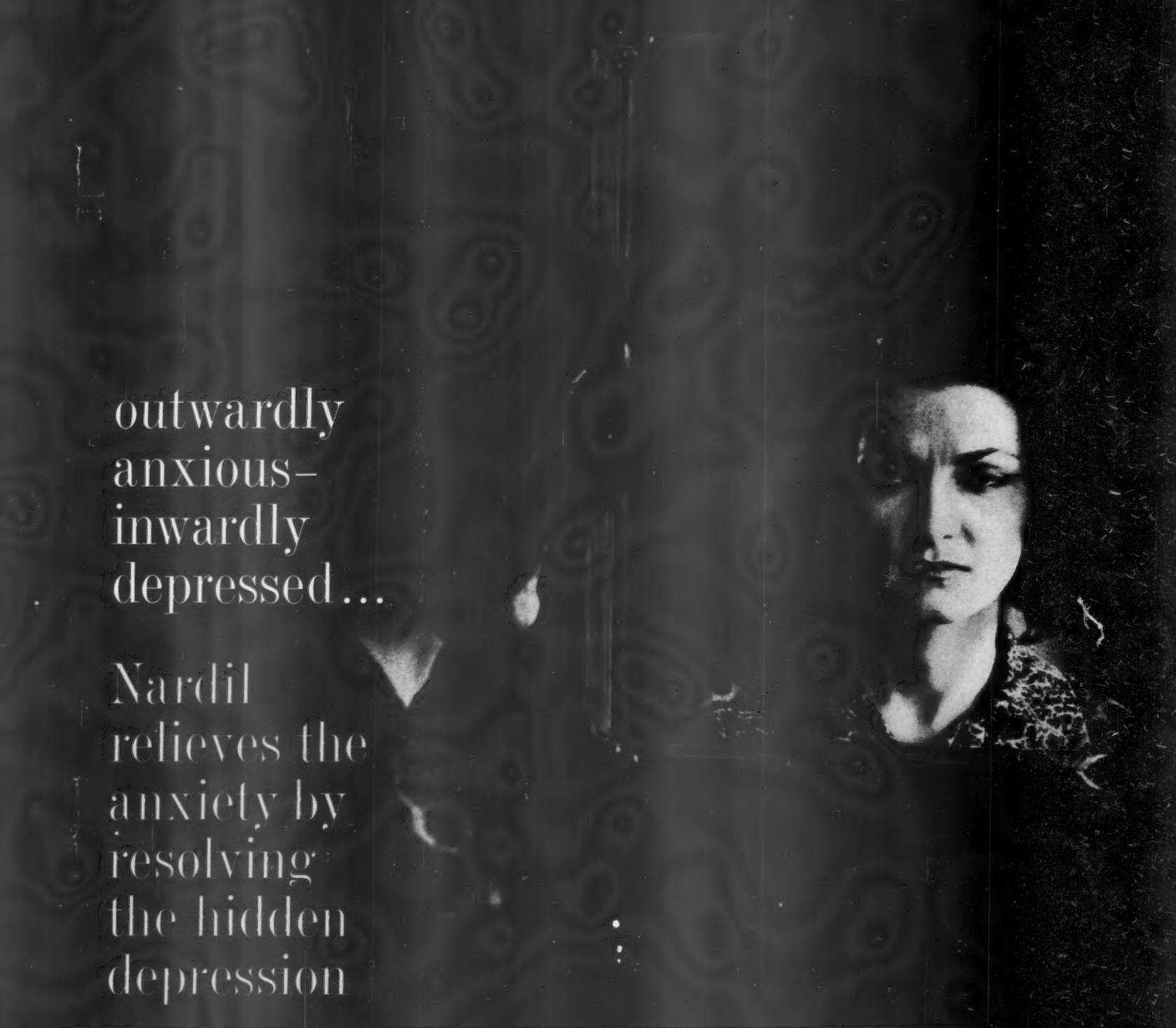
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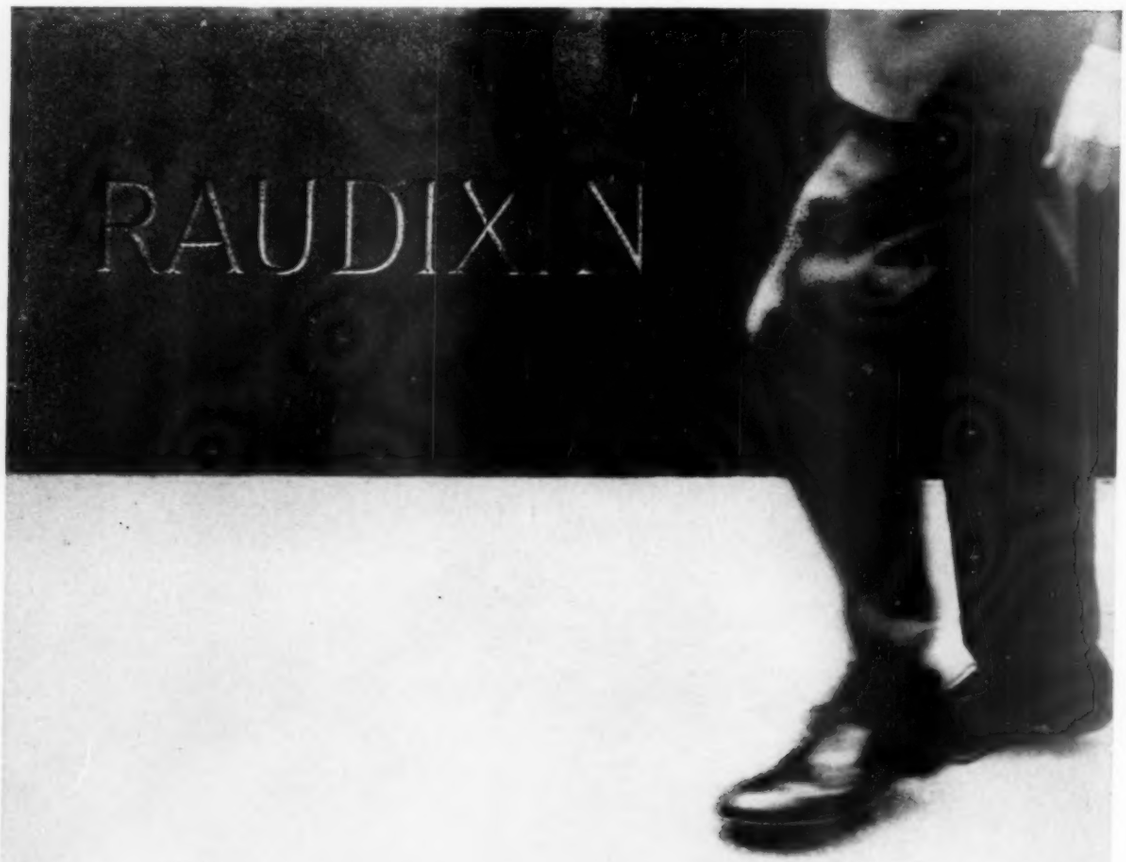
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Chronic Liver Disease in Young People. Clinical Features and Course in Thirty-Three Patients . . . . ROBERT G. WILLOCX AND KURT J. ISSELBACHER 185

This paper deals with the special problems of chronic liver disease, for the most part frank cirrhosis, occurring in the young, particularly in girls—a confused and controversial subject which has attracted wide interest in recent years. It is made clear, by histologic examination, that the cirrhosis in such cases is of the postnecrotic type, in no wise morphologically separable from postnecrotic cirrhosis in older subjects. The peculiarities of the course—a high incidence of fever, acne, striae, arthralgias, menstrual abnormalities, excessive hyperglobulinemia—are therefore referable to the age of the affected subjects and do not denote a distinct disease. Nor does the occasional association with a positive L. E. test result warrant the separate designation of "lupoid hepatitis" or, necessarily, the diagnosis of latent or overt systemic lupus erythematosus.

Fatty Liver Presenting as Obstructive Jaundice
HAROLD BALLARD, MICHAEL BERNSTEIN AND JOHN T. FARRAR 196

The point of this paper, that alcoholics may have steatosis sufficient to cause intrahepatic biliary tract obstruction, is supported by five case histories. Extrahepatic biliary tract obstruction may be simulated, and fruitless surgical intervention undertaken if one is unaware of this condition. With appropriate conservative management, the jaundice and associated abnormalities subside in due course.

Pulsations of the Liver in Heart Disease
HOMOBONO B. CALLEJA, OSCAR F. ROSENOW AND THOMAS E. CLARK 202

As explained herein, there is some point in reviving interest in registration of pulsations of the liver, as useful information can be obtained in relevant cases of heart disease. The discussion includes consideration of the "a" wave, due to atrial contraction, and the effects thereon of systolic or diastolic overloading of the right atrium, and the "v" wave, representing an increase in hepatic volume.

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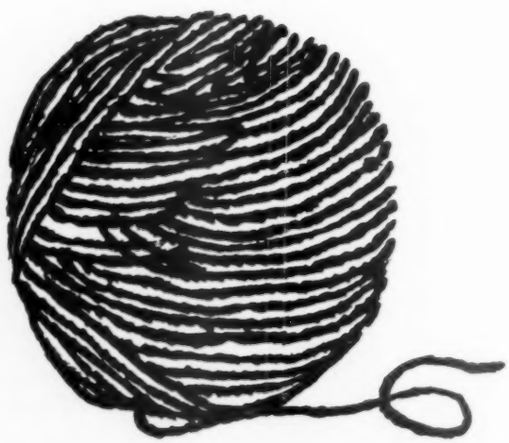
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*Duncan, G. G.: Diseases of Metabolism: Detailed Methods of Diagnosis and Treatment, ed. 4, Philadelphia, Saunders, 1959, p. 795.

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Alterations in Indices of Liver Function in Congestive Heart Failure with Particular Reference to Serum Enzymes

SIDNEY M. RICHMAN, ABNER J. DELMAN AND DAVID GROB 211

The authors have run through the gamut of "liver function" tests in 175 patients with acute and chronic heart failure of diverse etiology, and correlate the results with the etiologic, physiologic and morphologic factors involved. In acute, severe right heart failure the tests indicated damage to the hepatic parenchyma (which could be confirmed by direct examination of the liver showing centrilobular necrosis in many instances) and disturbed excretory function, particularly when the liver was markedly engorged. In chronic failure, or after multiple episodes of acute failure, the tests indicated less pronounced but more varied reactions. When recompensation occurred, most indices of liver function returned to normal.

Whipple's Disease. A Review of Twelve Patients from One Service

W. CROCKETT CHEARS, JR., MARION D. HARGROVE, JR., JOHN V. VERNER, JR., ALBERT G. SMITH AND JULIAN M. RUFFIN 226

A report on twelve proved cases of Whipple's disease, corroborating the recent experience that the diagnosis can be made during life, and indeed was in nine of these instances, and that the disorder, although of grave prognosis, is amenable to therapy. Most patients showed the characteristic syndrome of intermittent arthralgia, abdominal pain, diarrhea, weight loss, lymphadenopathy and intestinal malabsorption. The small bowel, on roentgenograms, showed the typical picture of malabsorption. The diagnosis could usually be confirmed by peripheral lymph node biopsy (PAS-positive material) or peroral biopsy of the intestinal mucosa. Treatment with combined antibiotic and steroid therapy seemed to give the best results. Five of the twelve patients in this series survived and were in good health.

Pulmonary Function in Asbestosis of the Lung. An Alveolar-Capillary Block Syndrome

MORTIMER E. BADER, RICHARD A. BADER AND IRVING J. SELIKOFF 235

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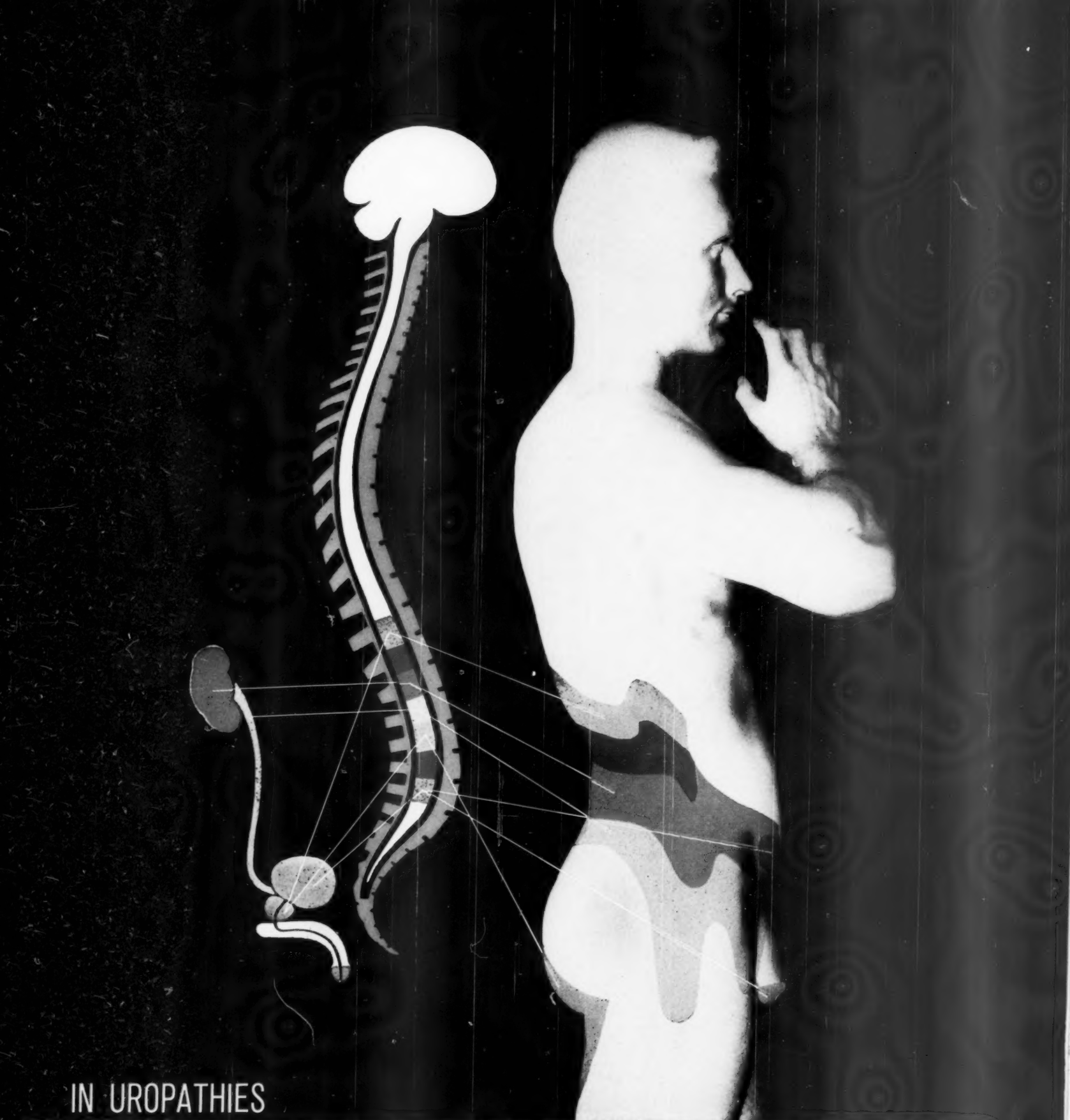
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The Veterans Administration-Army Cooperative Study of Pulmonary Function. I. Clinical Spirometry in Normal Men.

ROSS C. KORY, ROBERT CALLAHAN, HOLLIS G. BOREN AND MAJOR JAMES C. SYNER 243

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IN UROPATHIES

WHEN PAIN IS PART OF THE PICTURE

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Heat and Water Exchange in the Respiratory Tract
JAMES E. C. WALKER AND ROE E. WELLS, JR., WITH THE COLLABORATION OF EDWARD W. MERRILL 259

While it is generally appreciated that the respiratory tract plays an important role in heat and water exchange, the quantitative relations and sites of this important regulation are not well known. These are discussed in this interesting paper, together with the physical principles involved. In disease, particularly of the respiratory tract, the regulatory apparatus may be disturbed with important clinical consequences that are often ignored. The authors discuss in particular the effects of fever, hyperventilation, respiratory tract disease, tracheostomy and general anesthesia.

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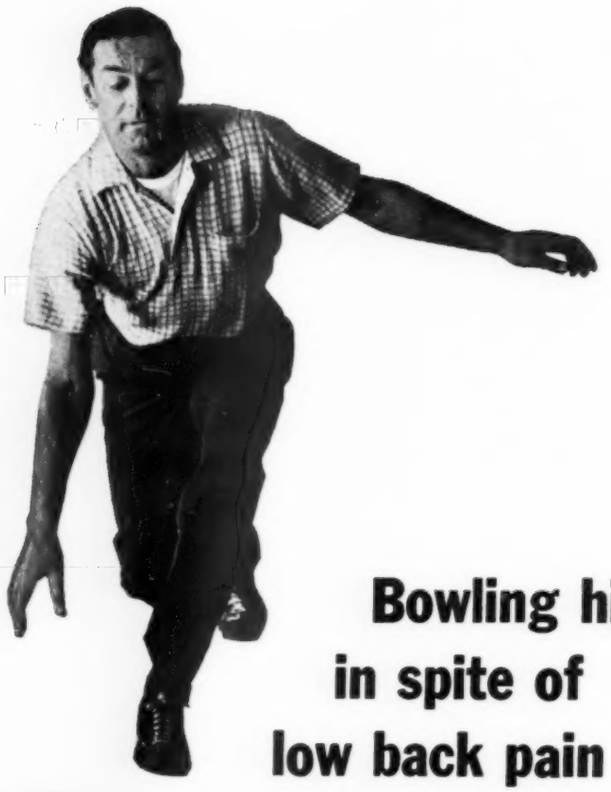
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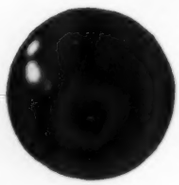
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1. Kearney, R. D.: *Current Therap. Res.* 2:127, April, 1960. 2. Cohen, A. I.: *Current Therap. Res.* 2:374, Aug., 1960.

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ROBIN D. POWELL, NANCY E. WARNER, ROBERT S. LEVINE AND JOSEPH B. KIRSNER 334

A case of unusual interest in which what appeared clinically to be quite typical non-specific ulcerative colitis turned out to be quite striking cytomegalic inclusion disease in the colon.

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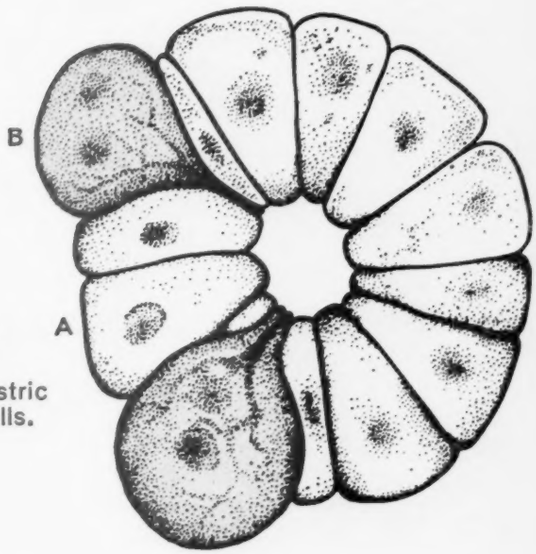
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References:

1. Douthwaite, A. H., and Hunt, J. N.: Effect of "Nacton" in Patients with Duodenal Ulcer, Brit. Med.J. *1*:1030-1034 (May 3) 1958. 2. Douthwaite, A. H.: The Development of the Treatment of Duodenal Ulcer, Proc. Roy. Soc. Med. *51*:1063-1068 (Dec.) 1958. 3. Steigmann, F.: The Problems of Side Effects in Anticholinergic Therapy, to be published. 4. Grossman, M. I., and Tuttle, S. G.: Clinical Report to McNeil Laboratories. 5. Texter, E. C.: Clinical Report to McNeil Laboratories. 6. Cayer, D., and co-workers: Clinical Report to McNeil Laboratories. 7. Lorber, S. H.: Clinical Report to McNeil Laboratories. 8. Walker, G. F.: Therapeutics; Gastric Sedatives, Brit. J. Clin. Pract. *13*:362 (May) 1959. 9. Douthwaite, A. H., Hunt, J. N., and MacDonald, I.: A Long-Acting Inhibitor of Gastric Secretion, Brit. Med. J. *2*:275-276 (Aug. 3) 1957.

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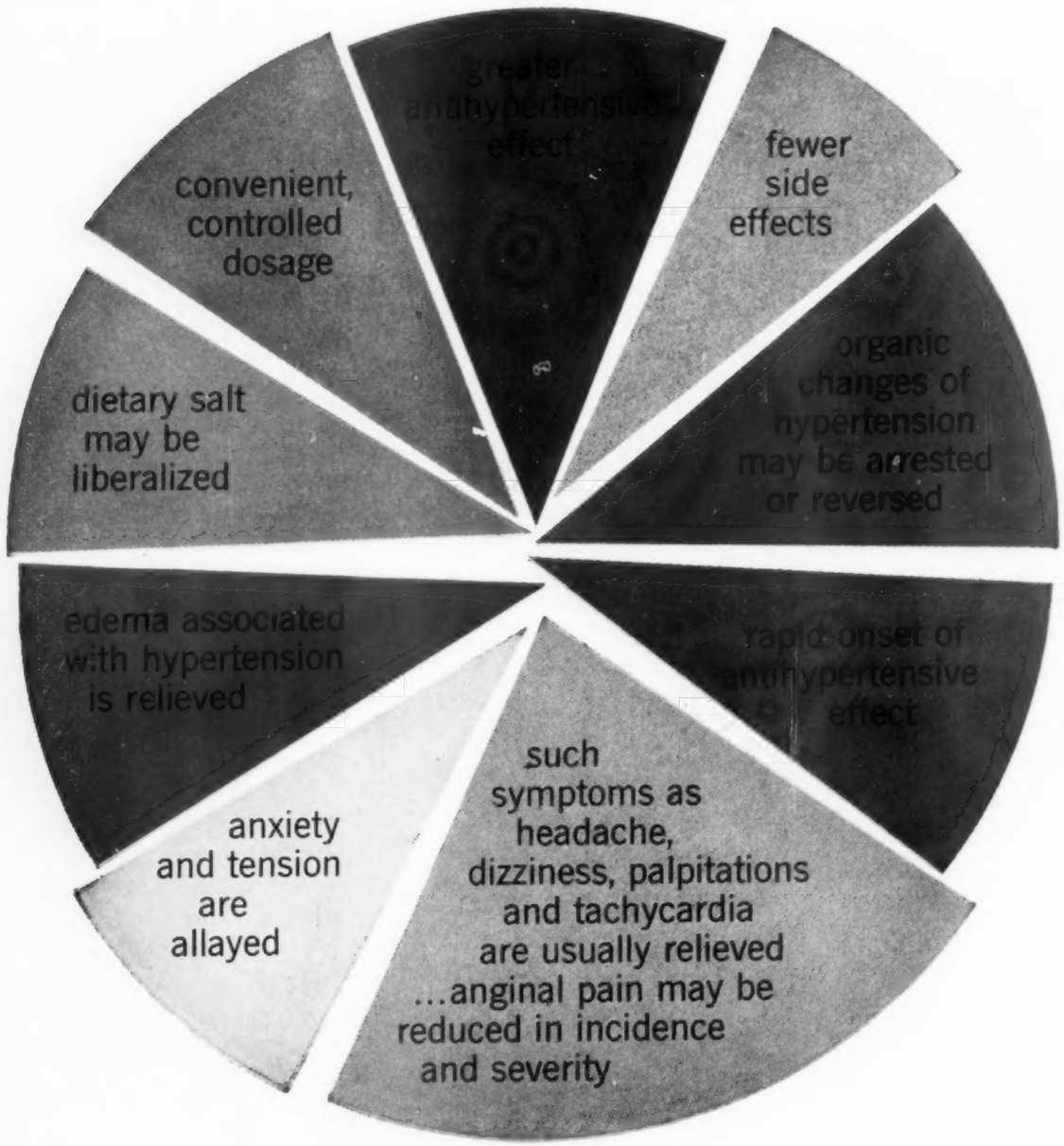
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ERYTHROPOIETIN FOUND TO CONTROL RED CELL FORMATION

A wealth of evidence now confirms the fact that red blood cell production is controlled by the hormone, erythropoietin.[1-3] Demonstrated in human plasma,[4] erythropoietin has shown its activity by producing reticulocytosis[1,5-7] increasing the uptake of Fe^{59} isotope in circulating red cells, and increasing erythrocyte precursors in marrow cultures.[3,8]

erythropoietin levels — new criteria in diagnosis of anemia Since erythropoietin is so rapidly used up in the process of erythropoiesis, increased erythropoietin blood levels can be demonstrated only in severe anemia or for a short time after the start of accelerated production.[9] Thereafter, the effect of the higher levels appears only as an increased erythroid marrow activity.[10] Since the hemopoietic marrow is capable of producing more red cells than normally required, it is postulated that many anemias may be due to inadequate erythropoietin levels—a result of subnormal production or excessive excretion.

how does erythropoietin affect iron metabolism? It is now well established that absorption and utilization of iron is dependent principally upon the degree of bone marrow erythropoiesis.[11,12] The rate of erythropoieses is, in turn, dependent upon erythropoietin levels. Thus, the demand for iron created by accelerated erythropoiesis is satisfied either by increased gastrointestinal absorption of iron or by mobilization of storage iron, or both. Failure to consider inadequate erythropoietin levels would seemingly account for the frequently disappointing results so often seen with the administration of iron alone in the treatment of anemia.

can erythropoietin levels be increased by medication? Cobalt has been shown to be strikingly effective in increasing the production of erythropoietin.[13,14] It is the only known therapeutic agent able to do this. Thus the effect of cobalt-enhanced erythropoietin improves iron utilization and causes a prompt and marked reticulocytosis with subsequent increase in hemoglobin and erythrocytes.

The new concepts of the cause, diagnosis, and management of anemia may now be applied clinically on the sound basis of extensive studies published on RONCOVITE®—MF, the therapeutic cobalt-iron hematinic.

(1) Gordon, A. S.: Pharmacol. Rev. **39**:1, 1959. (2) Erslev, A. J.: J. Lab. & Clin. Med. **50**:543, 1957. (3) Rosse, W. F., and Gurney, C. W.: J. Lab. & Clin. Med. **53**:446, 1959. (4) Gurney, C. W.; Goldwasser, E., and Pan, C.: J. Lab. & Clin. Med. **50**:534, 1957. (5) Rambach, W. A.; Alt, H. F., and Cooper, J. A. D.: Blood **12**:1101, 1957. (6) Gordon, A. S., **et al.**: Proc. Soc. Exp. Biol. & Med. **92**:598, 1956. (7) Erslev, A. J.: Blood **10**:954, 1955. (8) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L. F.: Blood **13**:55, 1958. (9) Stohlman, F., Jr., and Brecher, G.: Proc. Soc. Exp. Biol. & Med. **100**:40, 1959. (10) Kraus, L. M., and Kraus, A. P.: Fed. Proc. **18**:1051, 1959. (11) Bothwell, T. H.; Pirzio-Biroli, G., and Finch, C. A.: J. Lab. & Clin. Med. **51**:24, 1958. (12) Beutler, E., and Buttenwieser, E.: J. Lab. & Clin. Med. **55**:274, 1960. (13) Goldwasser, E.; Jacobson, L. O.; Fried, W., and Plzak, L.: Science **125**:1085, 1957. (14) Murdock, H. R., Jr., and Klotz, L. J.: J. Am. Pharm. A. (Scient. Ed.) **48**:143, 1959.

For a complete background file on erythropoietin, the erythropoietic hormone, please write to the Medical Service Department of:



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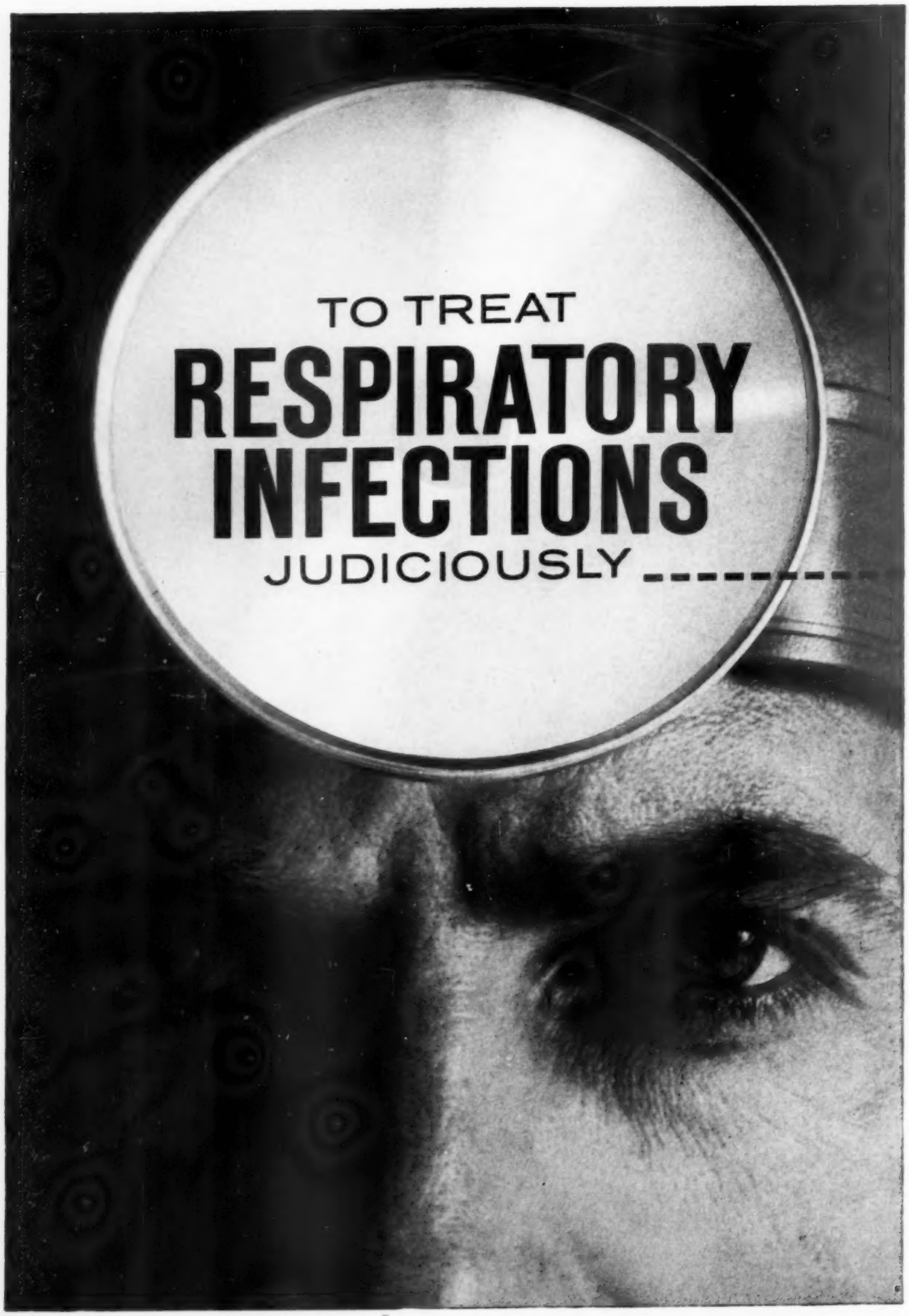
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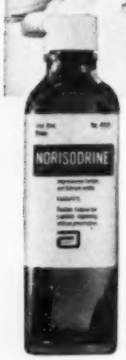
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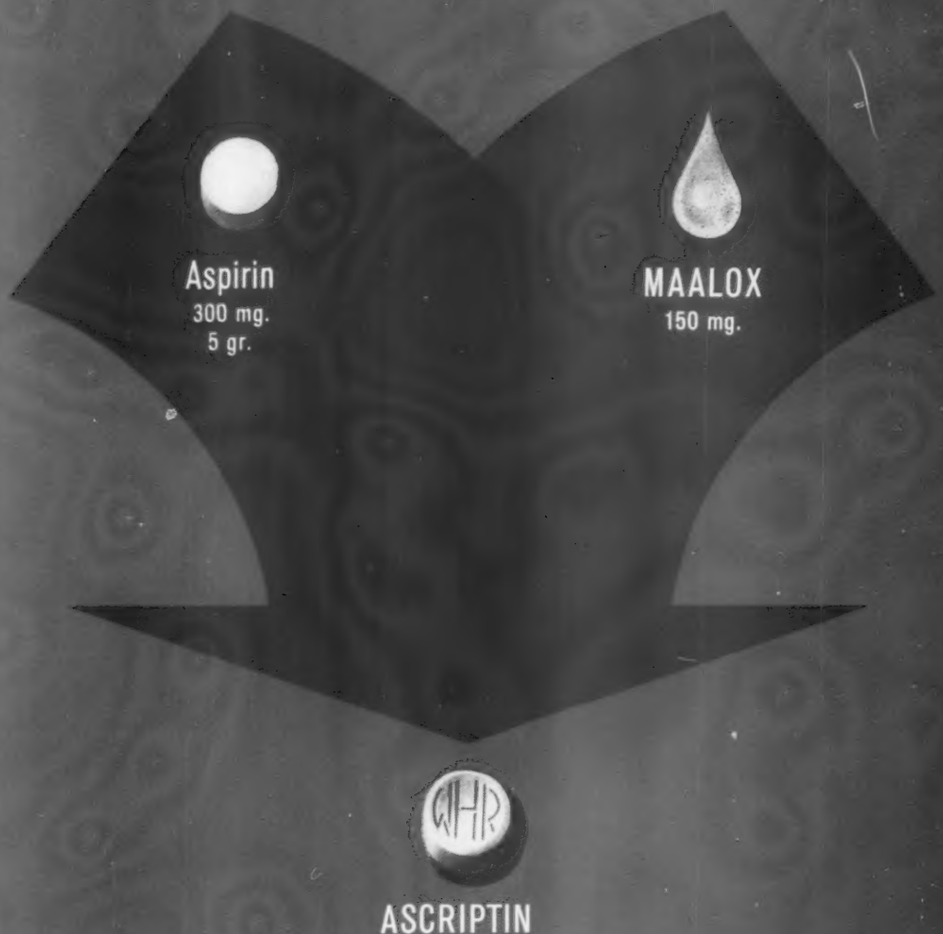
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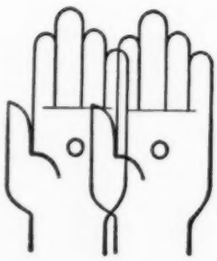
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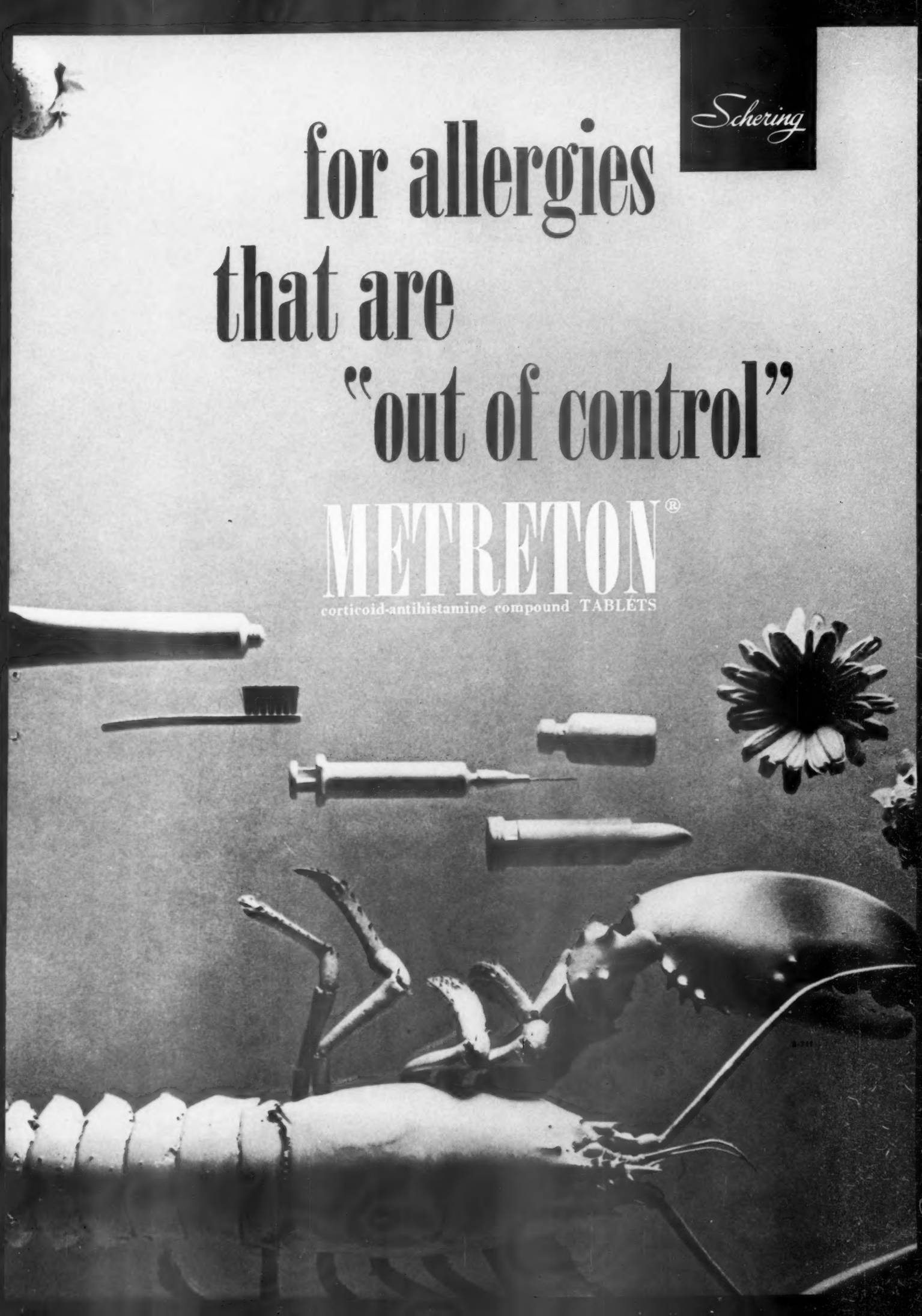
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Friedman, A. P., and Merritt, H. H.: J.A.M.A. *163*:1111 (Mar. 30) 1957.

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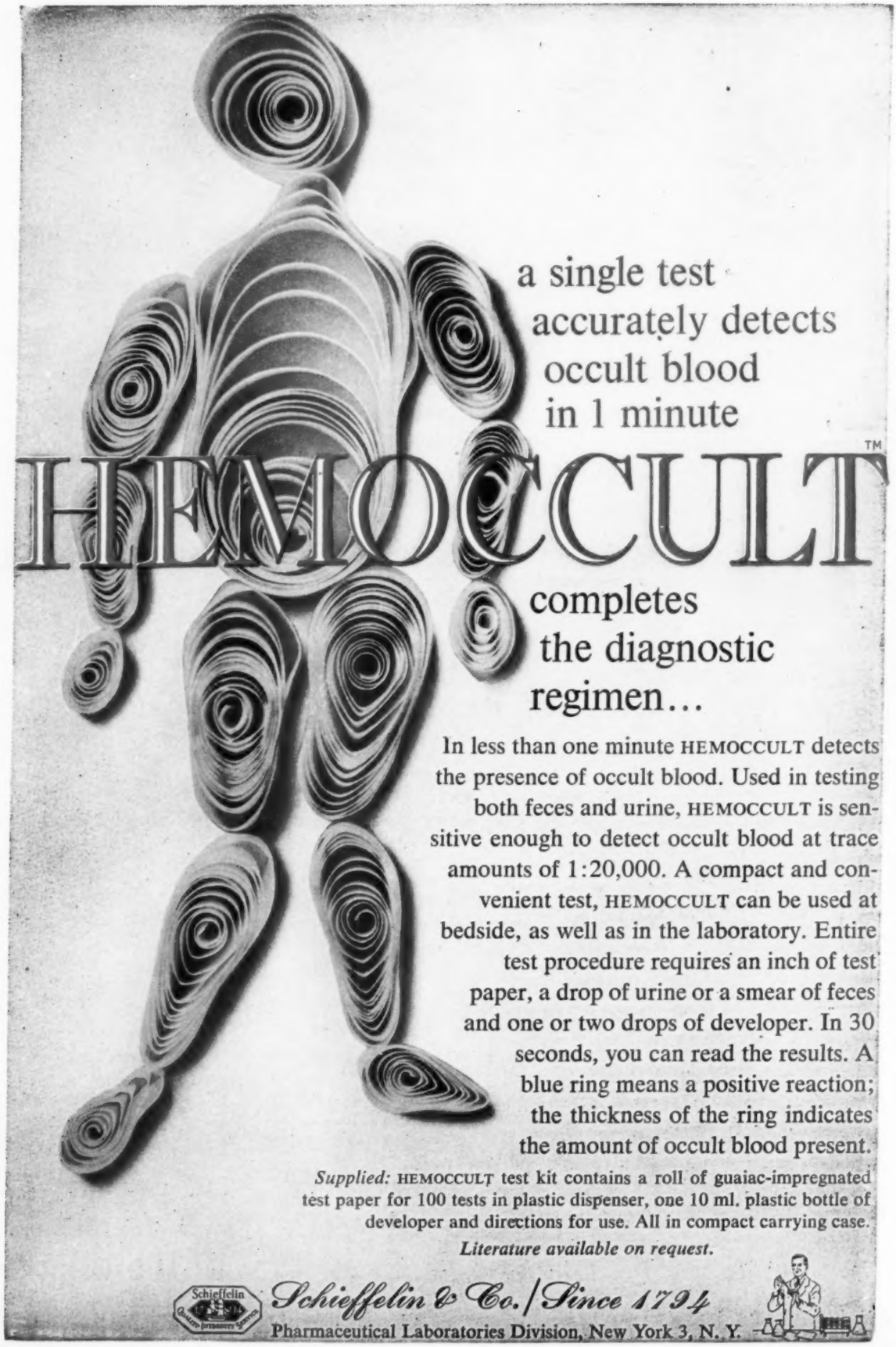
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1. California Med. *91*:327 (Dec.) 1959.
2. Clin. Res. *7*:388, 1959.

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BIBLIOGRAPHY 1. Ford, R. V., Clinical-Pharmacologic Investigation of Methyclothiazide, a New Oral Diuretic; Comparative Clinical Effects of Hydrochlorothiazide and Methyclothiazide, Current Therap. Res., 2:422-430, Sept., 1960. 2. Bryant, J. M., Schvartz, N., Fletcher, L., Jr., Fertig, H., Schwartz, M. S., McDermott, J. D., Quan, R., Clinical Studies of the Anti-hypertensive Effects of a New Benzothiadiazine Diuretic, submitted for publication.

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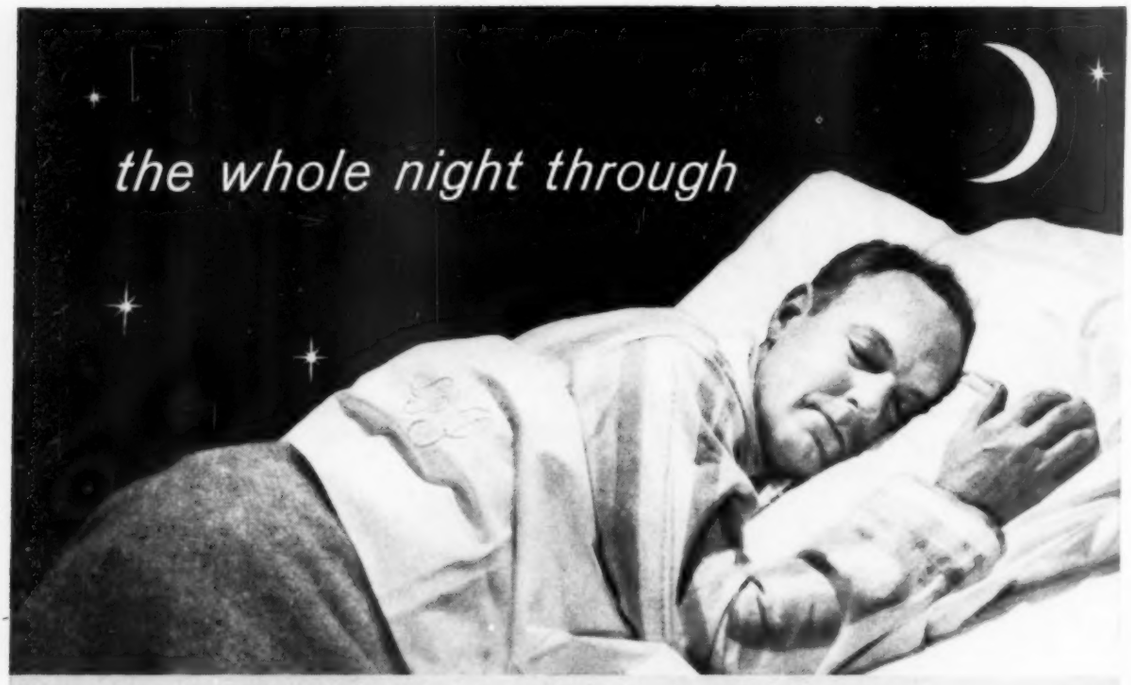
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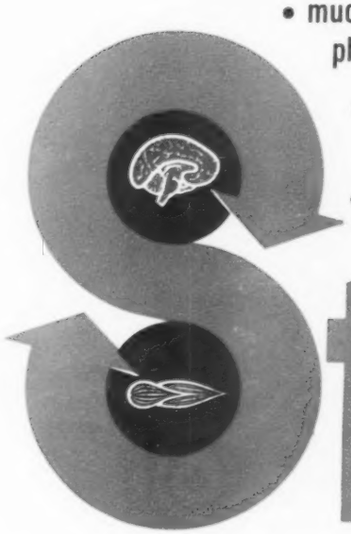
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1. Bellet, S., Finkelstein, D., and Gilmore, H.: A.M.A. Arch. Int. Med. 100:750, 1957.
2. Bellet, S.: Amer. Heart J. 56:479, 1958.
3. Finkelstein, D.: Penn. Med. J. 61:1216, 1958.
4. Bellet, S.: Amer. J. Cardiology 4:268. 1959.

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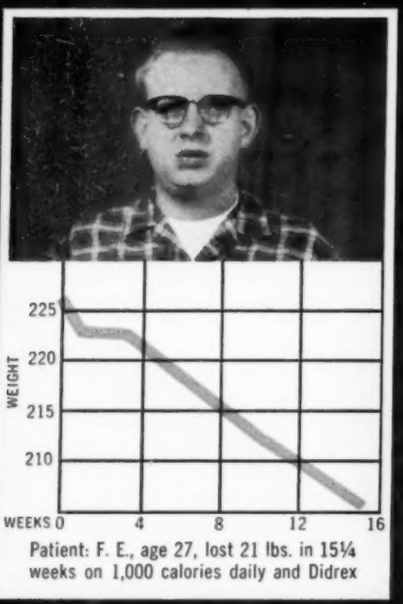
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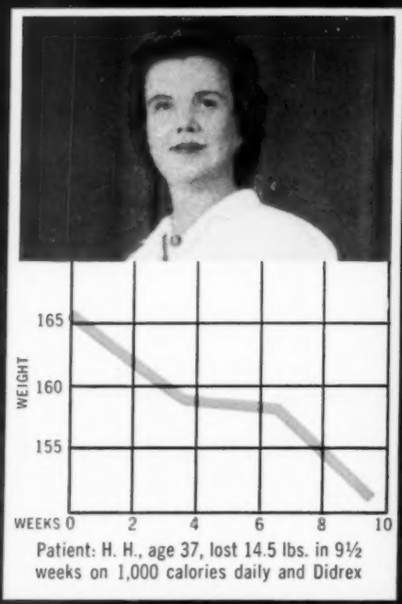
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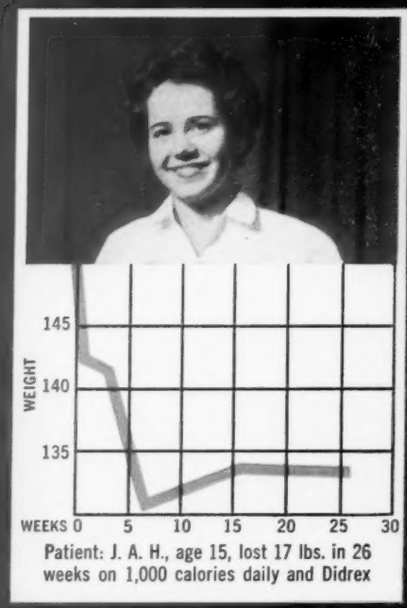
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References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex®). Journal of the Oklahoma State Medical Association, *53*:760-767 (November) 1960. 2. Oster, H., and Medlar, R.: A clinical pharmacologic study of benzphetamine (Didrex®), a new appetite suppressant. Arizona Medicine, *17*:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex®). Current Therapeutic Research, *2*:33-38 (February) 1960.

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disorders

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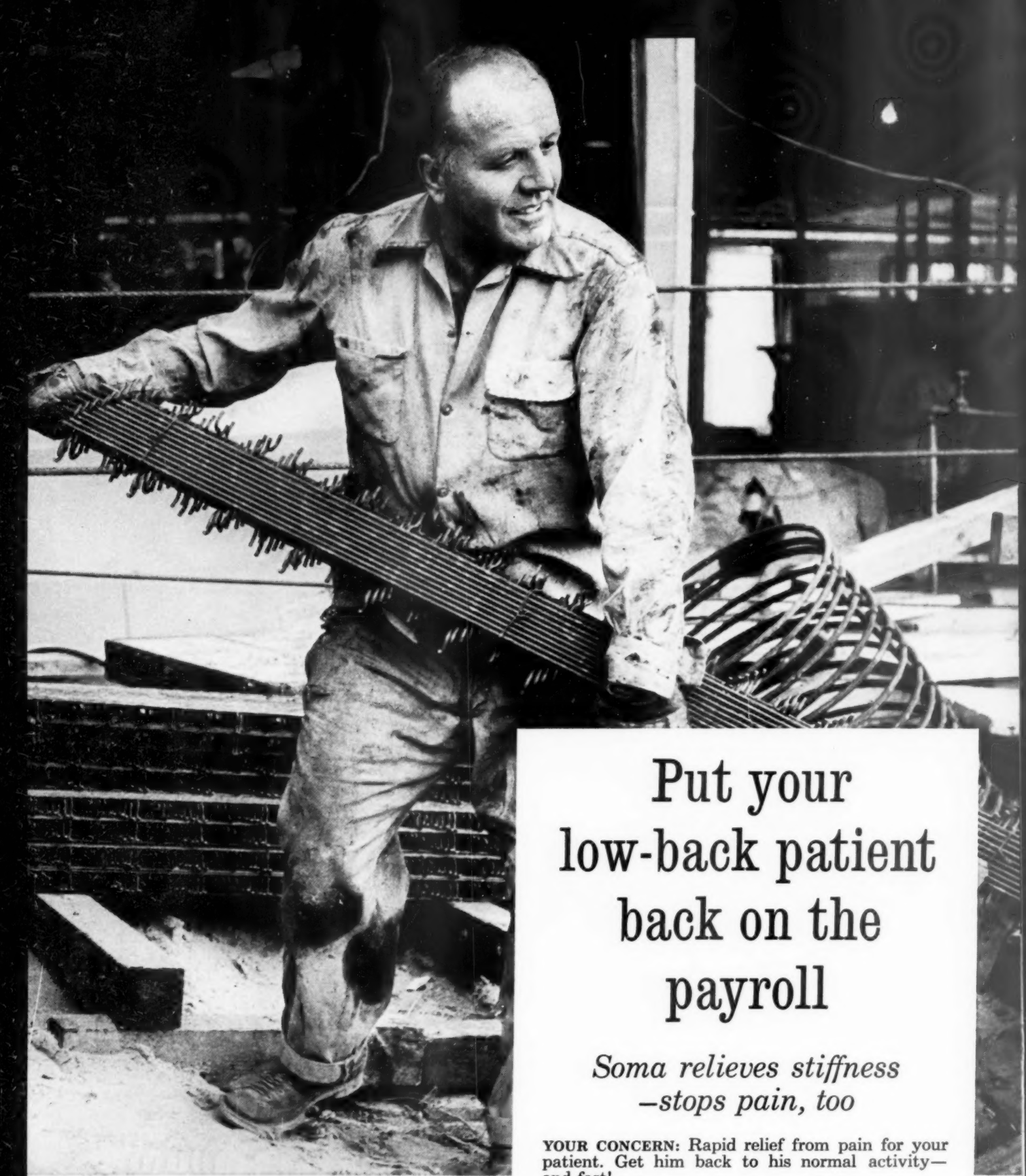
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DIMETAPP Extentabs contain Dimetane® (parabromdylamine [brompheniramine] maleate) 12 mg., phenylephrine HCl 15 mg., and phenylpropanolamine HCl 15 mg. Dependable Extentabs construction assures relief of symptoms for up to 12 hours with 1 tablet.

Dosage: Adults—1 Extentab q. 8-12 hours. Children over 6—1 Extentab q. 12 hours. Administer with caution to patients with cardiac or peripheral vascular diseases and hypertension, and to those sensitive to antihistamines. See package insert for further details. **Supplied:** bottles of 100 and 500.

*Full bibliography on Dimetane available on request.

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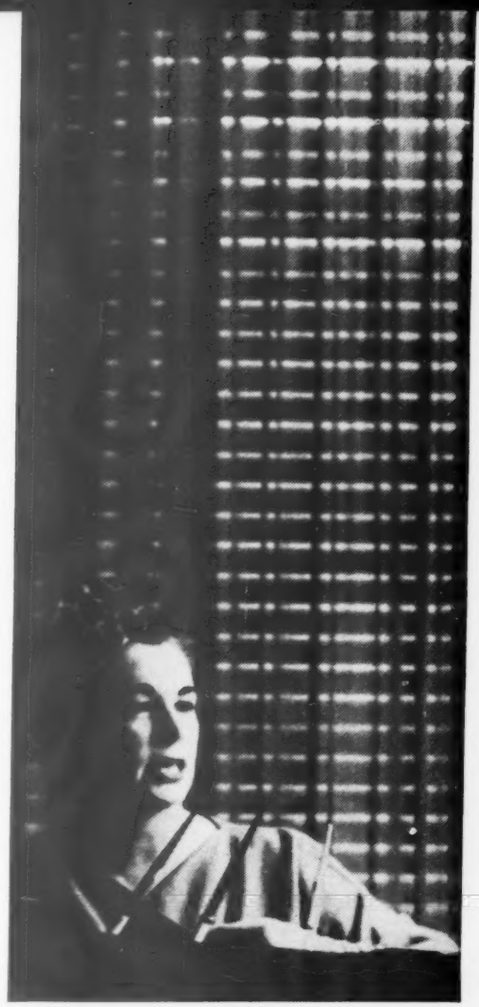
Soma is notably safe. Side effects are rare. Drowsiness may occur, but usually only in higher dosages. Soma is available in 350 mg. tablets. USUAL DOSAGE: 1 TABLET Q.I.D.

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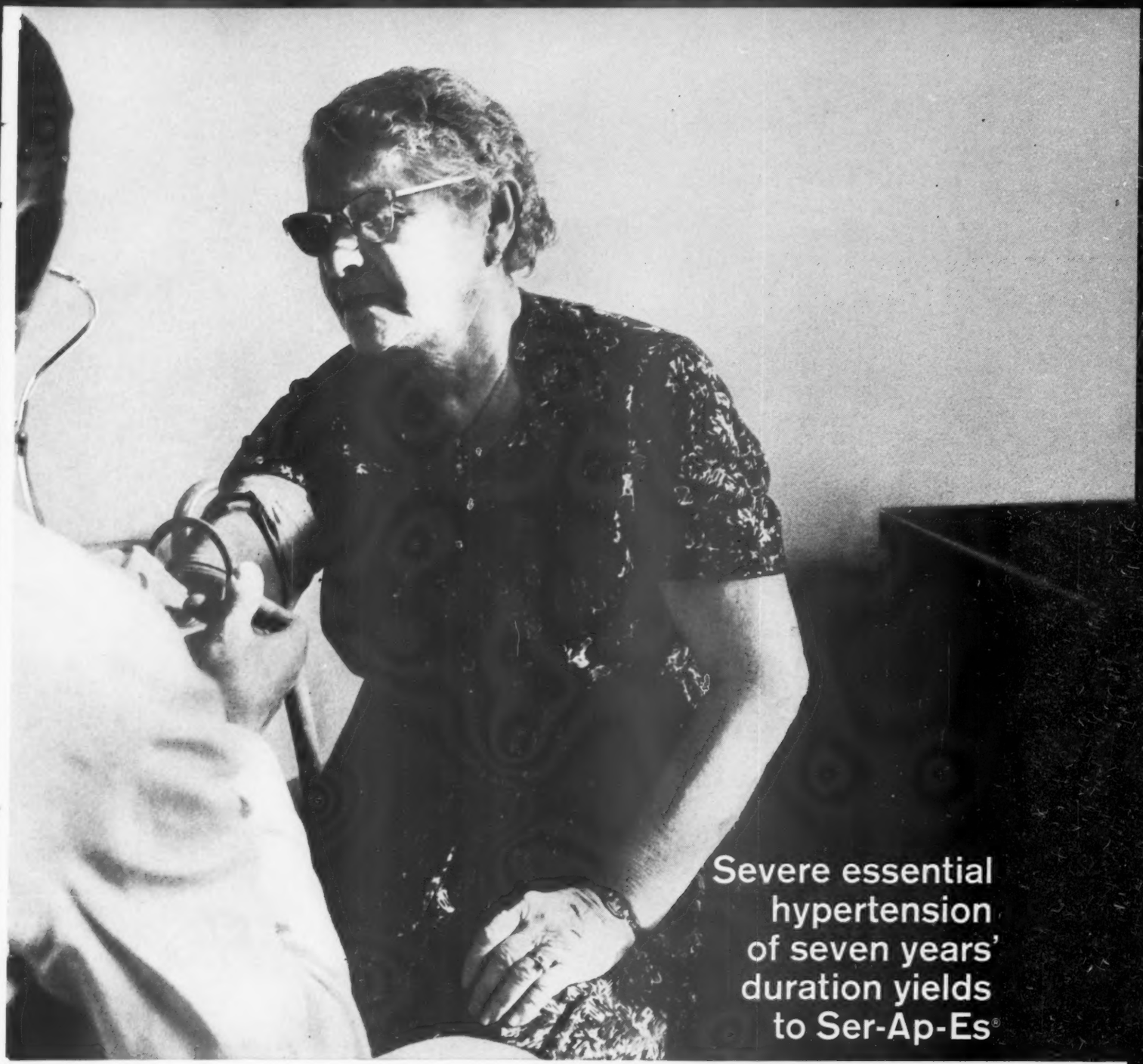
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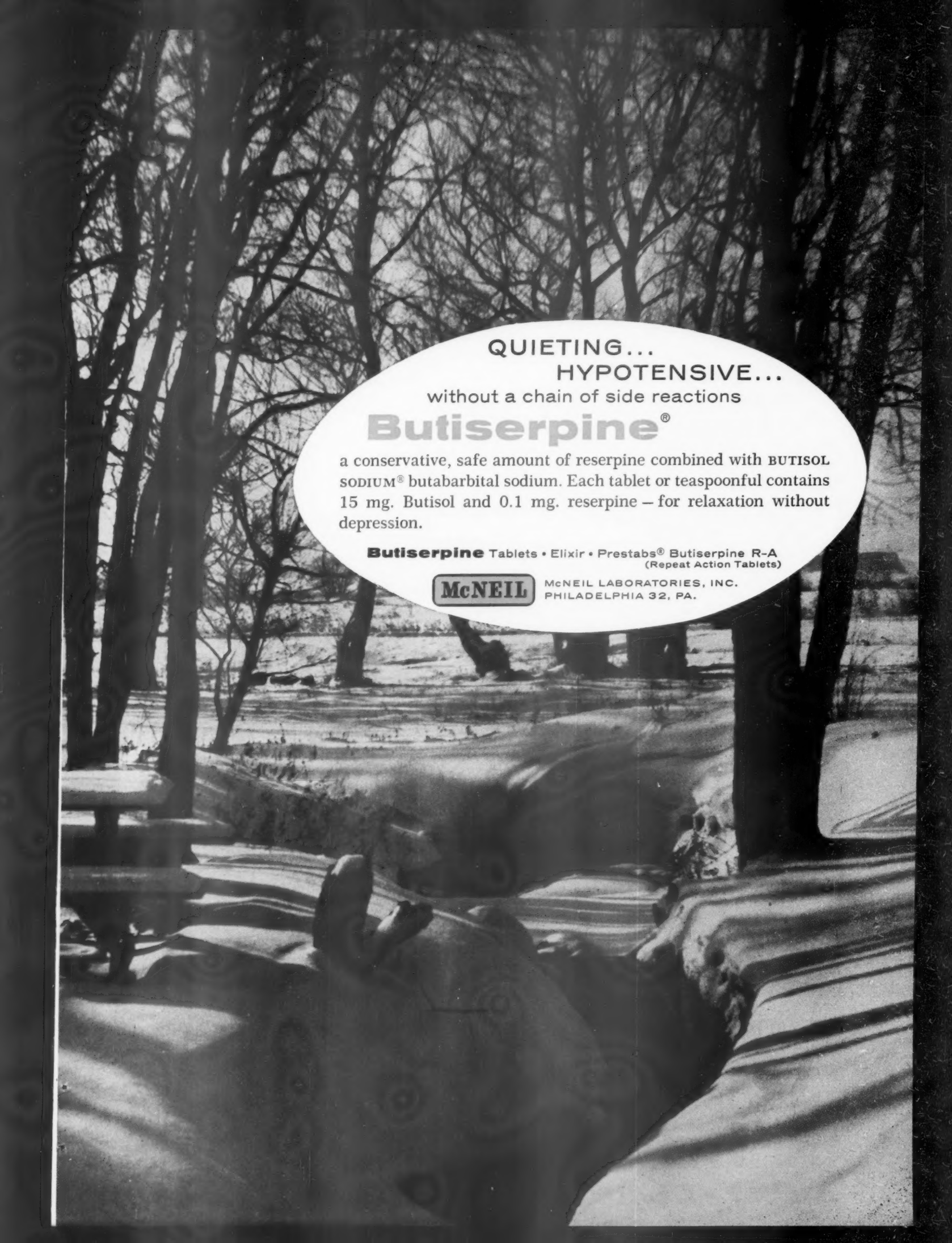
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in the cardiac or the hypertensive patient		allays anxiety without adverse influence on blood pressure[2]	helps correct certain functional arrhythmias, does not increase gastric secretion[2]
in problem drinkers		allays anxiety—makes patient more manageable[3]	produces no significant depression of blood pressure, pulse rate, or respiration. No liver involvement reported
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in pediatrics		allays tension in agitated, hyperkinetic patients	avoids danger of liver damage or other untoward reactions

References: **1.** Benson, C., and Benson, R. C.: Scientific Exhibit, Illinois Acad. Gen. Practice, Sept., 1960. **2.** Salmons, J. A.: Dis. Chest 38:105, 1960. **3.** Major, R. A.: GP 21:104, 1960. **4.** Grady, R. W., and Rich, A. L.: Scientific Exhibit, Am. Soc. Anesth., New York, Oct. 4-7, 1960.

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INDICATIONS: Vistaril is clinically effective in anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, pre- and postpartum and pre- and postoperative tension and emesis, certain functional arrhythmias, and pediatric behavior problems.

ADMINISTRATION AND DOSAGE: Dosage varies with the state and response of each patient, rather than with weight and should be individualized by the physician for optimum results. *Recommended oral dosage:* In anxiety and tension states, senility, alcoholism, pre- and postoperative and pre- and postpartum tension and emesis: up to 400 mg. daily in divided doses. In anxiety associated with asthma, neurodermatoses, menopausal syndrome, digestive disorders, functional or essential hypertension, tension headaches: 50 mg. q.i.d. initially—adjust according to response. In cardiac arrhythmias: initial—25 mg. q. 6 h. until arrhythmia disappears; maintenance or prophylactic—50-75 mg. daily in divided doses. In pediatric behavior problems under 6 years: 50 mg. daily in divided doses. Six and over: 50-100 mg. daily in divided doses. *Recommended parenteral dosage:* In preoperative, obstetrical, and more emergent situations in other indications: 25-100 mg. I.M. or I.V. q. 4 h., p.r.n. In cardiac arrhythmias: 50-100 mg. I.M. stat, and q. 4-6 h., p.r.n.; maintain with 25 mg. b.i.d. or t.i.d.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgement of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL *Capsules* (hydroxyzine pamoate)—25, 50, and 100 mg. VISTARIL *Oral Suspension* (hydroxyzine pamoate)—25 mg. per 5 cc. teaspoonful. VISTARIL *Parenteral Solution* (hydroxyzine hydrochloride)—10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc.

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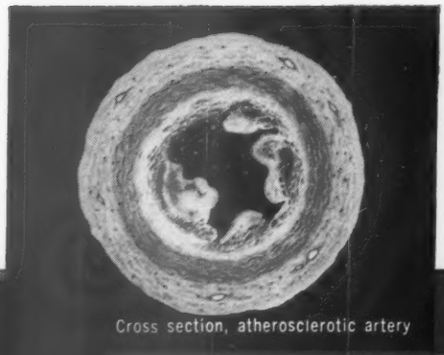
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References: **1.** Cohen, A., et al.: J.A.M.A. 165:225, 1957. **2.** Spies, T. D., et al.: J.A.M.A. 159:645, 1955. **3.** Stecher, R. M.: Panel Discussion, Ohio M. J. 52:1037, 1956.

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Vitamin A	1870 USP units
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Calories	415

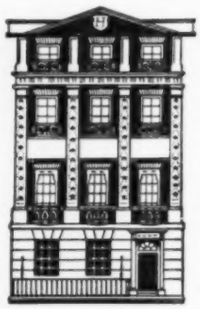
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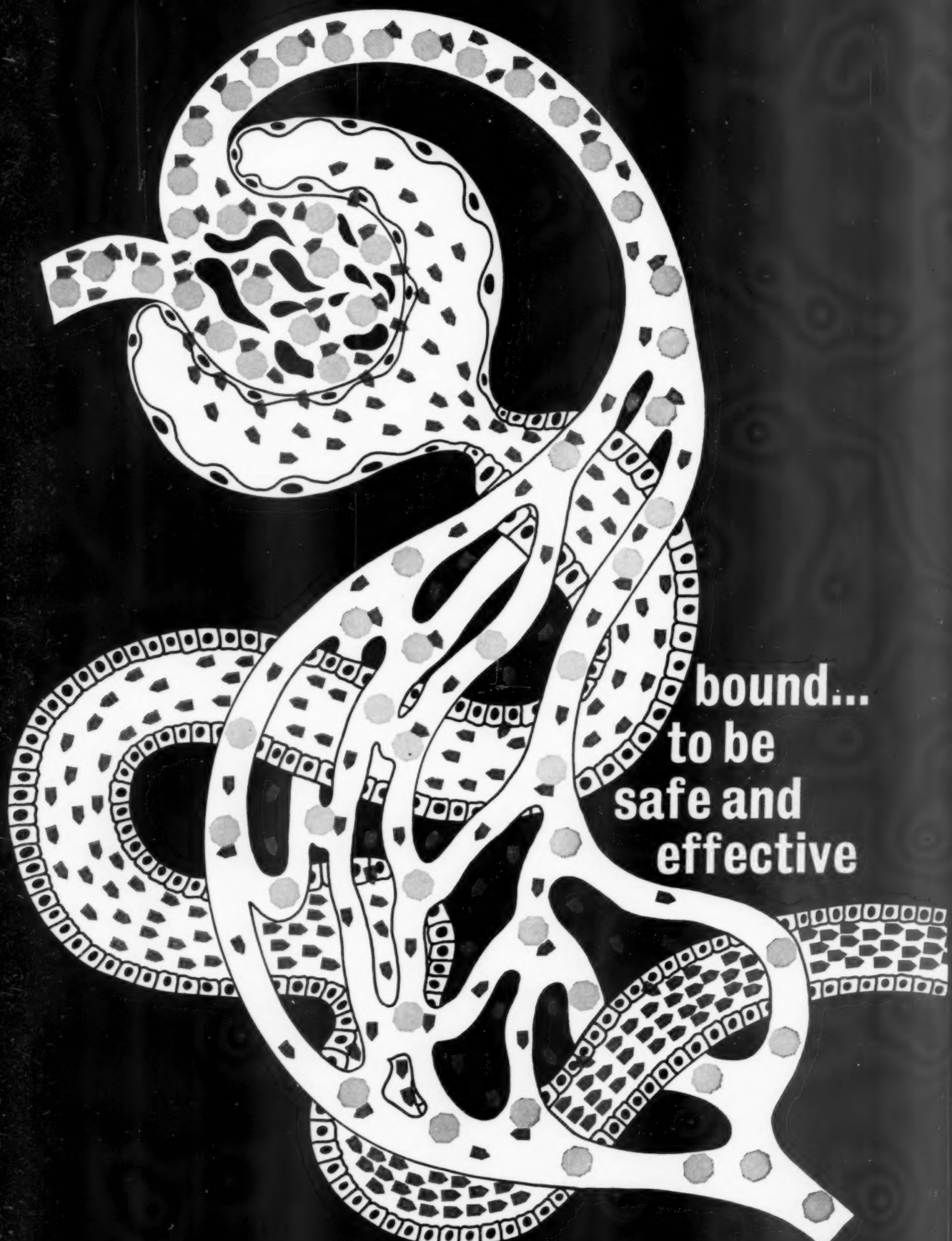
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REFERENCES: 1. Thompson, I. M.: Family Physician, Chicago 9:14, 1959. 2. Campbell, M. F.: Mod. Med. 24:85, 1956. 3. Paul, M. F., et al.: Am. J. Physiol. 197:580, 1959. 4. Johnson, S. H., III, and Marshall, M., Jr.: J. Urol., Balt. 82:162, 1959. 5. Lippman, R. W., et al.: J. Urol., Balt. 80:77, 1958.

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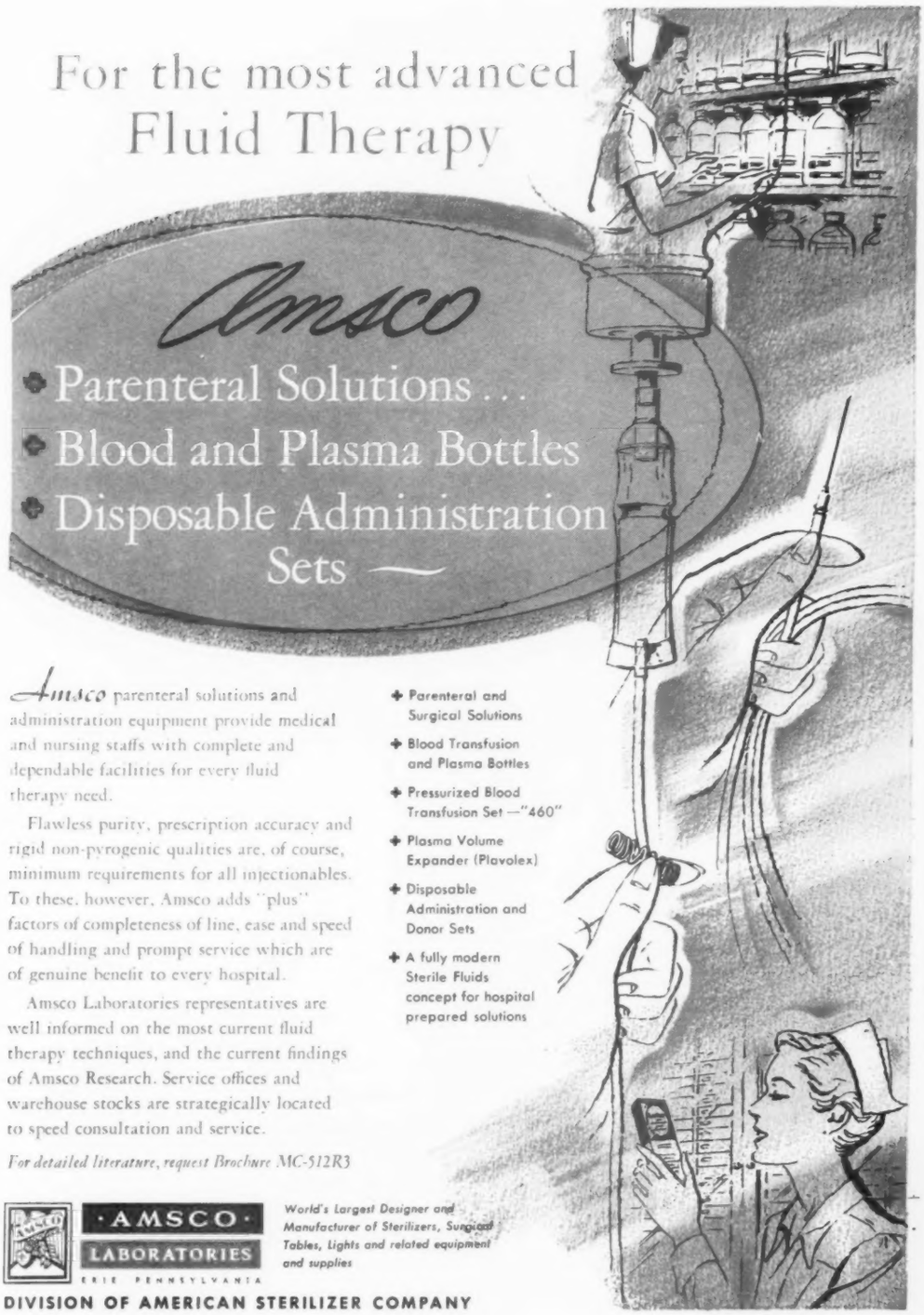
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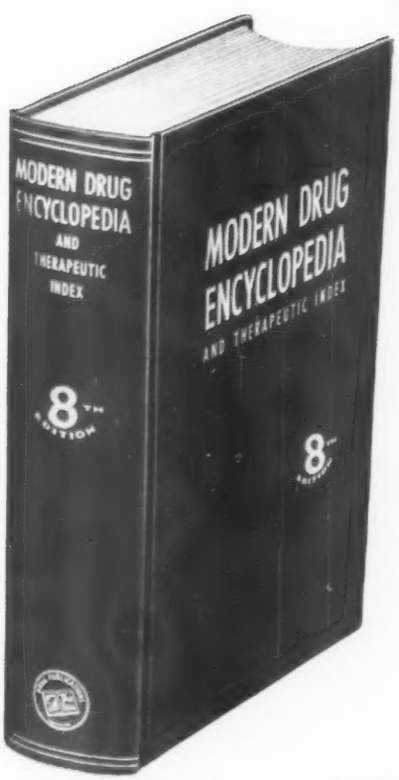
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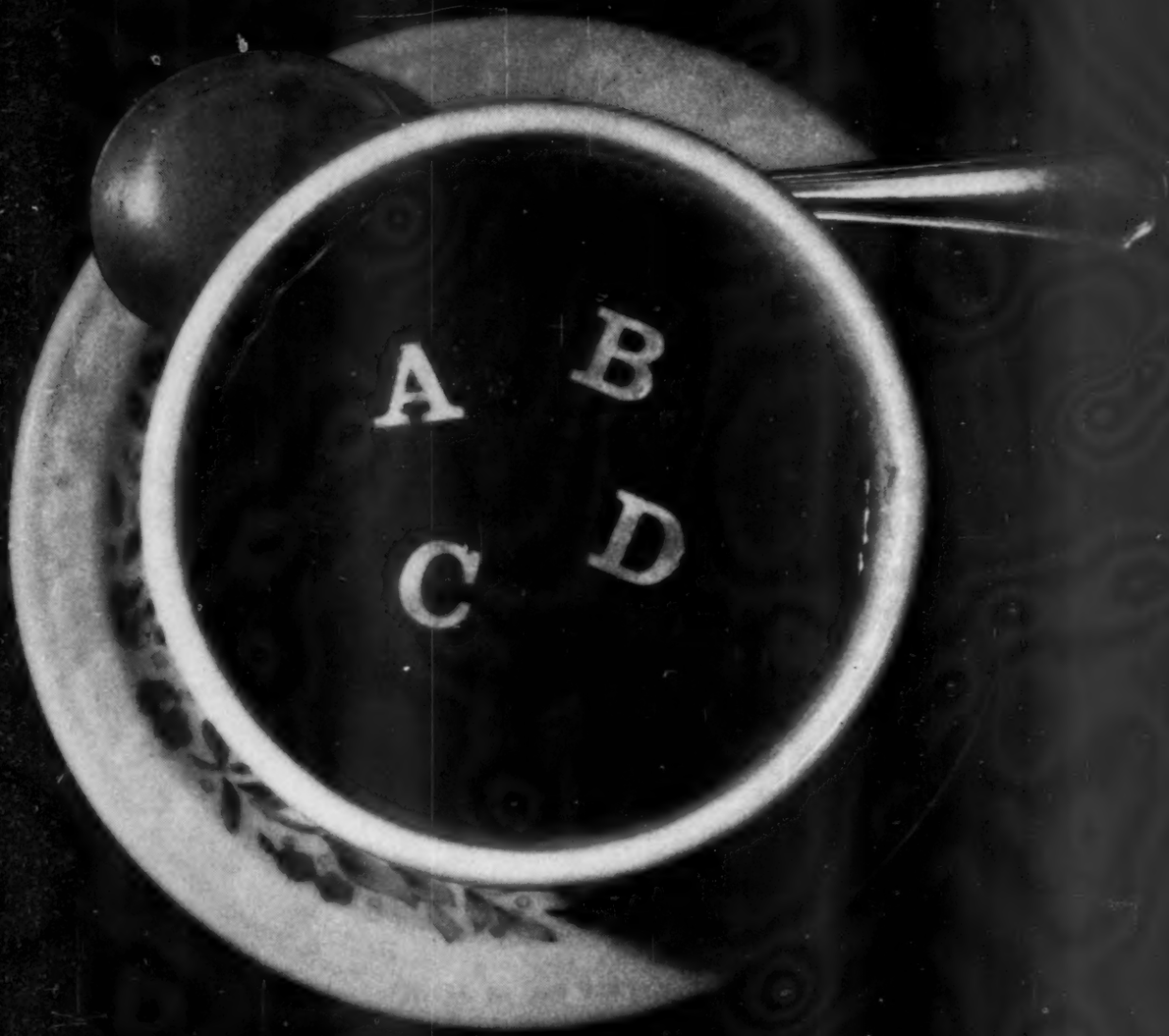
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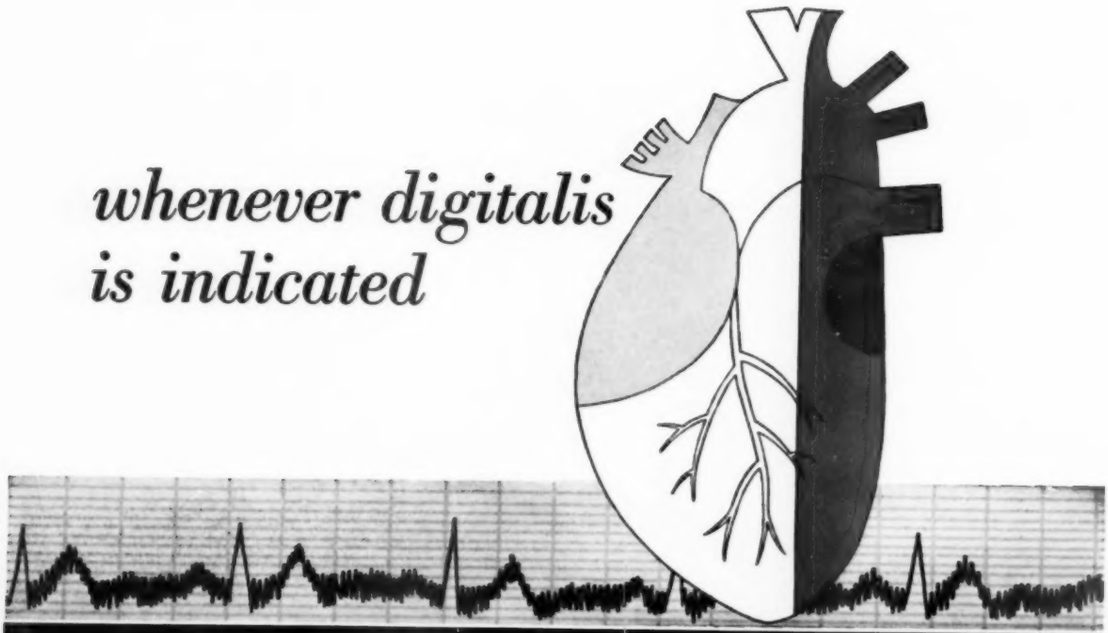
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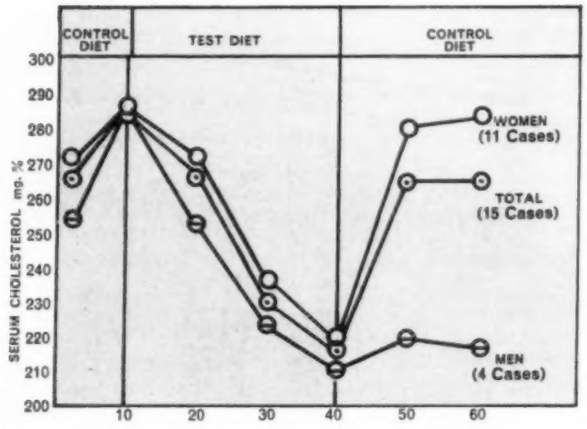
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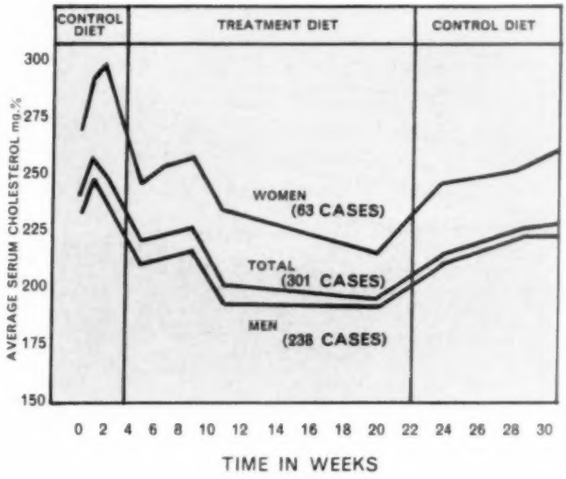
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References: 1. Terman, L. A.: Geriatrics *14*:111 (Feb.) 1959. 2. Boyer, P. A.; Lowe, J. G.; Gardier, R. W., and Ralston, J. D.: J.A.M.A. *170*:257 (May 16) 1959.

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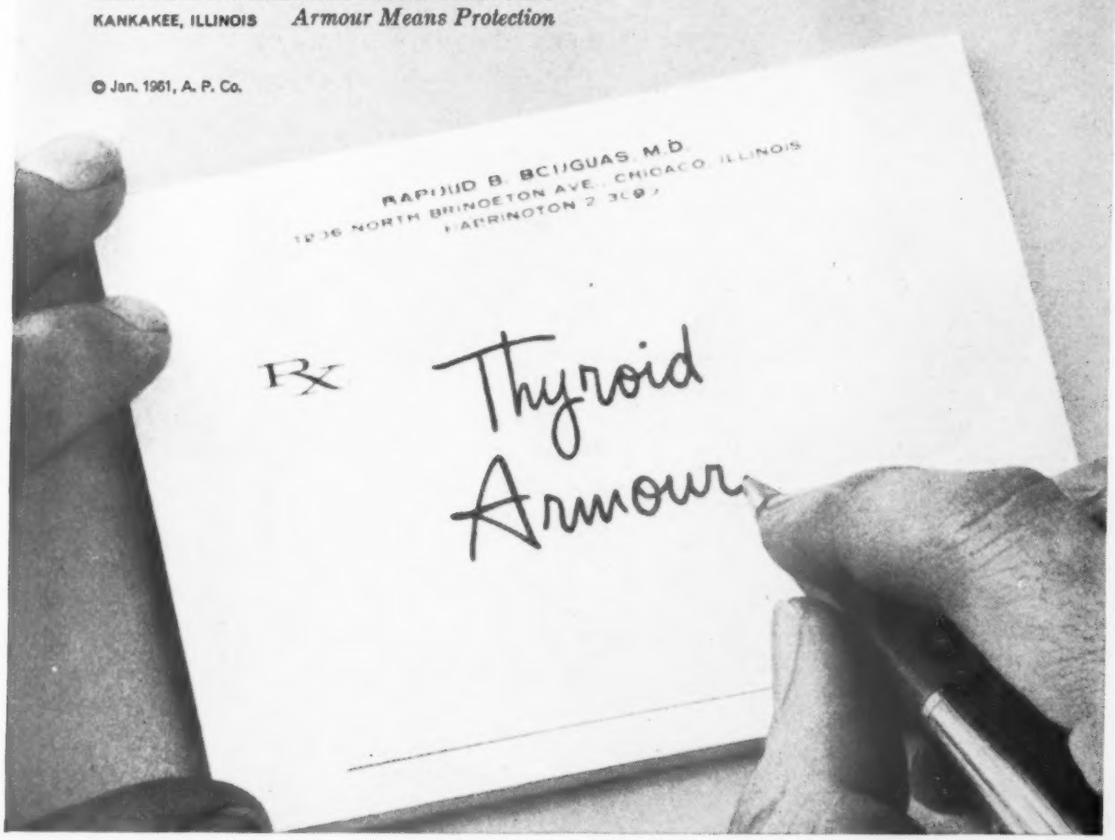
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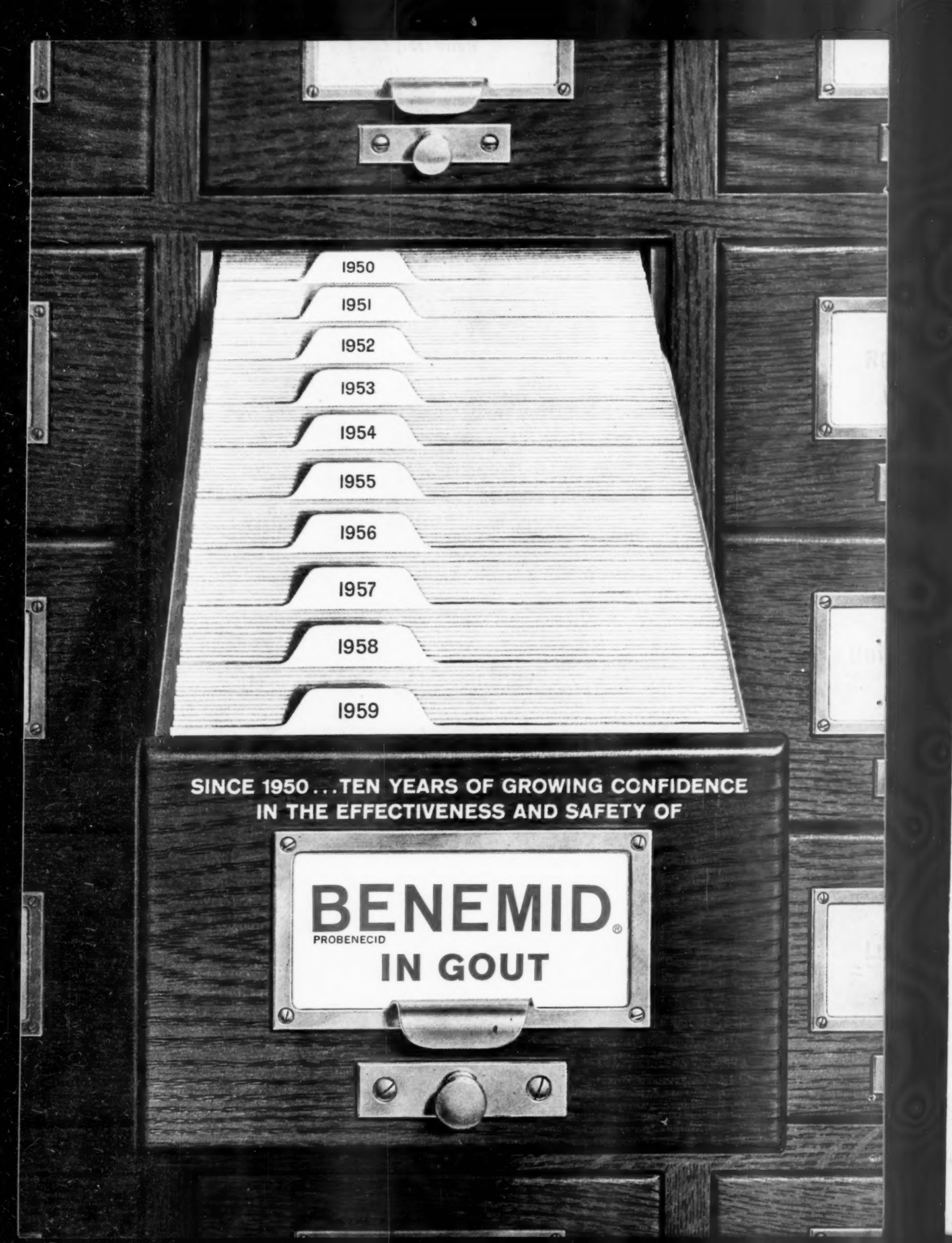
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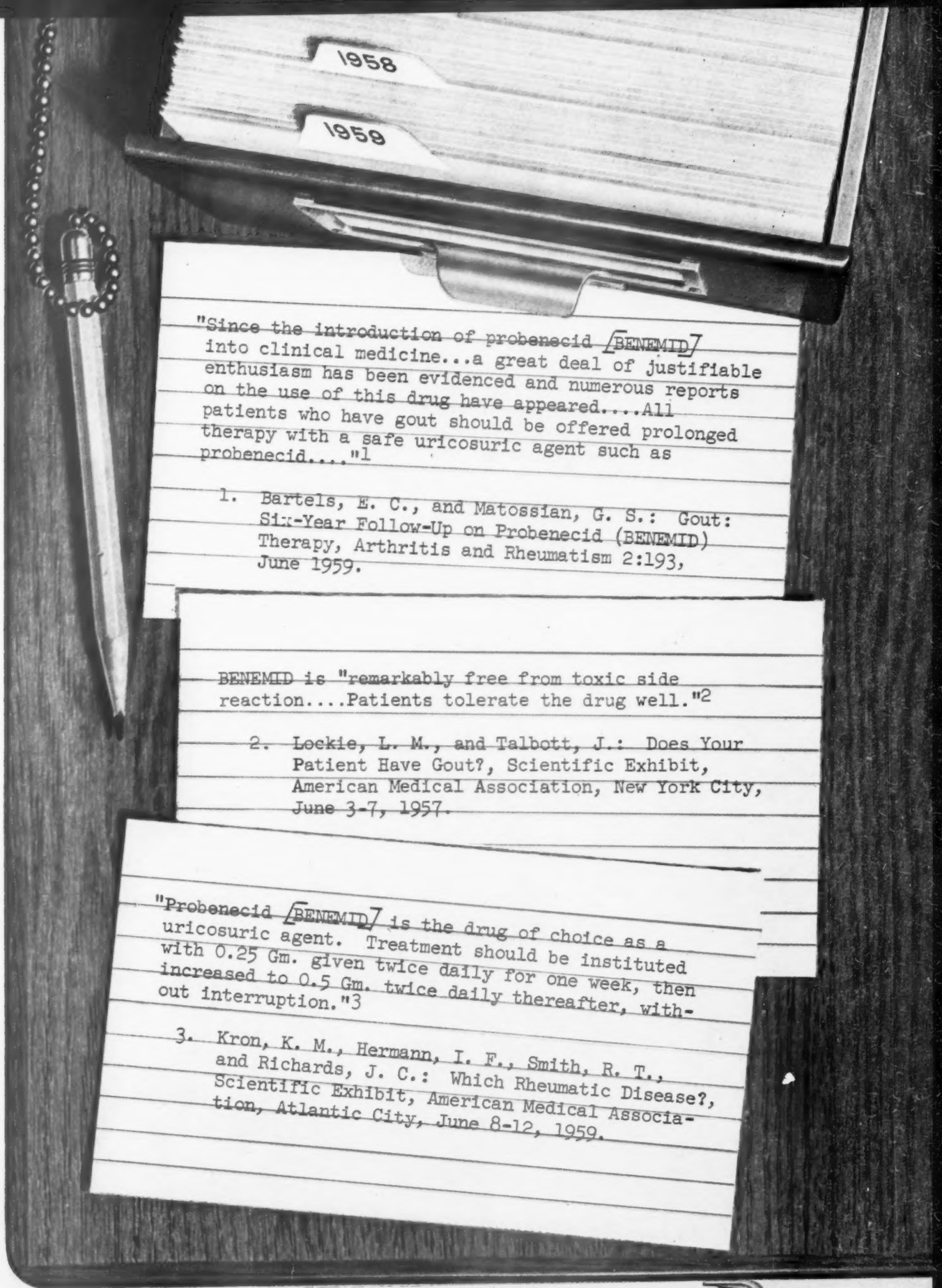
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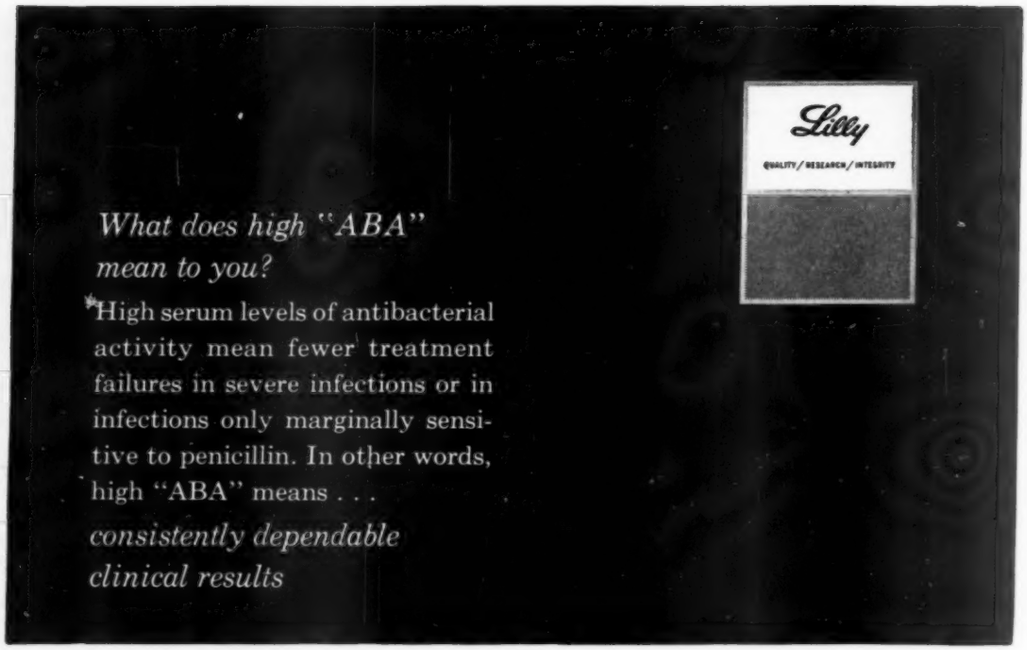
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1. McCarthy, C. G., and Finland, M.: Absorption and Excretion of Four Penicillins, New England J. Med., *263*:315, 1960. 2. McCarthy, C. G., Hirsch, H. A., and Finland, M.: Serum Levels after Single Oral Doses of 6-(α-phenoxypropionamido) Penicillanate and Penicillin V, Proc. Soc. Exper. Biol. & Med., *103*:177, 1960. 3. Griffith, R. S.: Comparison of Antibiotic Activity in Sera after the Administration of Three Different Penicillins. Antibiotic Med. & Clin. Therapy, *7*:129, 1960. 4. Editorial: New England J. Med., *263*: 361, 1960. 5. Editorial: New York J. Med., *60*:498, 1960.

The American Journal of Medicine

VOL. XXX FEBRUARY, 1961 NO. 2

Editorial

The Toxemias of Pregnancy and the Renal Lesion of Pre-eclampsia*

Such a loosely used and inclusive term as toxemias of pregnancy can no longer be regarded as precise or specific. It should be subjected to critical analysis, perhaps dissected out until there is nothing left.
W. W. HERRICK, 1938 [1].

FOR many years the term "toxemias of pregnancy" has been used to describe a multitude of disorders in the pregnant woman. More recently its use has been somewhat restricted, and to most obstetricians and internists nowadays it encompasses only pre-eclampsia and eclampsia,† hypertensive vascular disease in pregnancy, and renal diseases complicating the pregnant state.

In 1843 John Charles Lever,‡ a flamboyant *bon vivant* but a popular and successful London obstetrician, first associated a "highly albuminous" urine with convulsions in pregnant women. Lever was a contemporary of Richard Bright at Guy's Hospital, and described quite accurately the clinical course of eclampsia. In his paper [2] he recorded that the albuminuria rapidly diminished or disappeared if the patient survived the convulsions. He also recognized that the fits were not necessarily associated with uremia and, in fact, he used crude biochemical analyses of the blood to prove his point. The differentiation of the renal disorder which appears late in pregnancy from that which was present before conception was made four years earlier by Rayer [3].

During the ensuing century there has been little clarification of the etiology and pathogenesis of eclampsia, and perhaps even less

† It is conventional to use the term "eclampsia" if convulsions occur in pregnancy or the puerperium. "Pre-eclampsia" is used to describe a disease specific to pregnancy which includes edema, hypertension and/or proteinuria, provided that convulsions do not supervene.

‡ Samuel Wilks, who recognized and described the visceral manifestations of syphilis in 1863, wrote a vivid, succinct, but rather unkind biographical sketch of J. C. Lever in his "Biographical History of Guy's Hospital" (Ward, Lock, Bowden & Co., London, 1892). "Dr. Lever was known essentially as a practical man, and his lectures were characterised by their practical aim. They were clear and forcible, and upon the whole good. Never pretending to be scientific, he added to the literature of his subject by some good papers; more especially by his discovery of albumen in the urine in cases of puerperal convulsions. Having once started in practice, his rise was rapid: his consulting rooms were crowded to overflowing, and he for a time almost monopolised the practice in the southern suburbs of London. It was difficult to find a person of the female sex who had not consulted Lever, and no carriage was better known than his with its red borderings and red wheels, which gave it the popular appellation of 'Lever's fire-engine.' He gained the confidence of women more, perhaps, by his seeming power than by any pleasant manner; yet so infatuated were they with him, that a number of them united to have his bust taken by Baily, which they afterwards presented to him. At the height of his fame he took a countryhouse, bought horses for his children, and launched out in a more lavish way of living; he became a *bon vivant*, and ceased to be a teetotaller."

* This study was supported in part by grant H-5011 from the U.S. Public Health Service, Bethesda, Maryland.

understanding of the effects of pregnancy on renal disease. This has been due, perhaps, to the fact that hypertension, proteinuria and edema—the cardinal clinical phenomena of pre-eclampsia—are common findings, either severally or in combination, in women whose pregnancy is complicated by underlying renal disease or "essential" hypertension. And the dilemma which confronts the clinician in making an exact clinical diagnosis at the height of the illness stems from his knowledge that similar symptoms and signs may be manifestations, and indeed the sole manifestations, of three groups of diseases which separately and together complicate pregnancy. Indeed many clinicians do not attempt to distinguish clearly between them, resting content with the incomplete diagnosis, "toxemia." It is not surprising, therefore, that "such a loosely used and inconclusive term as toxemia of pregnancy" survives in widespread use today.

Because of the diagnostic difficulties at the bedside and because so many people have taken sides about the etiology, pathology, pathogenesis, treatment and outcome of pre-eclampsia, Fishberg [*4*] was moved recently to remark that "the nature of the nephropathies of pregnancy remains one of the most obscure chapters in the entire subject of Bright's disease." These considerations led us in 1954 to apply the technic of percutaneous needle biopsy of the kidney to a study of the renal lesions of pregnant women ill with hypertension, edema and proteinuria. In this way, intrinsic renal diseases, such as glomerulonephritis and pyelonephritis, were recognized readily during life, and the lesions in the small arteries and arterioles characteristic of hypertensive vascular disease were diagnosed. Moreover, studies of the tissues removed by biopsy revealed a unique and distinctive renal glomerular lesion, peculiar to pre-eclampsia and eclampsia, which allowed us to make accurate diagnoses of pre-eclampsia on histologic grounds alone [*5*].

Many pathologists who have investigated the problem state that the glomerular capillary basement membrane is thickened in eclampsia and report that similar lesions have been present in occasional patients who have died with pre-eclampsia. Allen, in his textbook on renal pathology [*6*], crystallized the views of this school of thought. He considered glomerulonephritis to be the common lesion in pre-eclampsia and eclampsia, and he stated that the acute membranous change he saw was " . . . histologically and physiologically indistinguishable from the early states of chronic membranous glomerulonephritis (i.e., the nephrotic form of glomerulonephritis or 'lipoid nephrosis' occurring without pregnancy)." But our studies do not support this thesis.

Renal biopsies were performed in fifty patients ill with toxemia of pregnancy, and exact histologic diagnoses were made in all [*7*]. Ten patients had evidence of hypertensive vascular changes in their kidneys, and primary renal disease was found in five. In the remaining thirty-five patients the lesions of pre-eclampsia were delineated. In these subjects the glomeruli were enlarged, swollen and ischemic. The glomerular involvement was widespread, and all glomeruli were similarly altered throughout the sections. Edema of the cells of the glomerular tuft was the most prominent pathologic feature; the edema affected both endothelial and epithelial cells, the former more severely. The swollen and increased endothelial cytoplasm encroached upon the lumen of the glomerular capillaries, thus contributing to the striking ischemia of the glomerular tuft. In addition, slight degenerative changes were seen in the tubules. The lesions were found in both pre-eclampsia and eclampsia, but have not been observed in any other disease affecting the kidney. The nature of the unique glomerular changes was confirmed by electron microscopic study. When the renal biopsies were repeated some weeks after delivery it was obvious that the glomeruli and tubules had returned to normal; the edema of the capillary wall had disappeared, and ischemia was not present.

On the other hand, in hypertensive vascular disease coincident with pregnancy, arterio- and arteriolosclerosis were found in the small vessels in the renal parenchyma, but the glomeruli were normal; moreover, they were not ischemic, and there was no edema of the glomerular capillary wall. After delivery there was no change in the histologic appearance. Pre-eclampsia and hypertensive vascular disease were found not to be necessarily mutually exclusive entities. In eight of the thirty-five patients with histologic evidence of pre-eclamptic glomerular lesions there was also histologic evidence of underlying arteriolosclerosis and hypertensive vascular disease. These lesions persisted after delivery. However, by the time the second biopsy specimen was obtained the

typical lesion of pre-eclampsia, viz., swelling of endothelial and epithelial cells of the glomerular tuft, had disappeared.

Clinical diagnoses were recorded on all patients before the renal biopsies were performed and these were reviewed in the light of the exact histologic diagnoses. Correct clinical diagnoses were made in thirty-six of the fifty patients. Since the presence of underlying hypertensive vascular disease was not suspected in most of the eight patients with histologic evidence of both pre-eclampsia and underlying hypertensive vascular disease, accurate and complete clinical diagnoses were made in only twenty-nine of fifty patients.

Once the nature of the histologic picture in pre-eclampsia had been accurately delineated, we found that the sections of kidneys from these patients could be readily grouped into three grades of severity. When this was done, all the clinical measurements and laboratory findings collected during pregnancy were plotted separately against each grade of pathologic change assigned to each section, in an attempt to find, retrospectively, some clinicopathologic correlations which might be useful diagnostically. Clinical and histologic data were also plotted for all patients with underlying hypertensive vascular disease, and control clinical and biochemical data were obtained from thirty healthy pregnant women in the last trimester of normal pregnancy.

The levels of diastolic and systolic blood pressure, changes in hematologic constants, levels of serum electrolytes and nitrogenous substances, and degree of proteinuria, among other measurements, did not appear to be useful diagnostic indices of pre-eclampsia. Thus far, only the level of the serum uric acid* and the presence of spasm of the retinal vessels appear to be helpful.

The serum uric acid level was 3.57 $\pm$ 0.69 mg. per 100 ml. in the control group of thirty healthy pregnant women in the last trimester of pregnancy. Similar values were recorded in patients with hypertensive vascular disease. In thirty-five patients in whom the diagnosis of pre-eclampsia was made on the basis of the findings in the renal biopsy specimens, the serum uric acid level was 6.43 $\pm$ 1.74 mg. per 100 ml. The difference between the pre-eclamptic group on the one hand, and the healthy pregnant women or the group with renal or vascular disease on the other, was highly significant. The uric acid level was elevated above the upper limits of normal for the third trimester of healthy pregnancy in 83 per cent of the patients with pre-eclamptic renal lesions, but in only 20 per cent of those with hypertensive vascular disease—the highest level recorded in the latter patients was 5.2 mg. per 100 ml. There was also an excellent correlation between the severity of the renal lesions and the level of the serum uric acid found in pre-eclampsia, since the uric acid level increased significantly with increasing severity of the renal lesions. The reasons for this increase in the serum uric acid level in pre-eclampsia are not yet clearly understood.

Spasm of the retinal arterioles, first described by Mylius [*8*] and Wagener [*9*], was the most striking physical finding in the patients with pre-eclamptic renal lesions. Retinal arteriolar spasm occurred in thirty of the thirty-five patients; it was widespread throughout the eyegrounds in some patients, but segmental and variable spasm of the arterioles was seen more frequently. The degree of retinal arteriolar spasm was found to be a rough indicator of the severity of the underlying pre-eclamptic glomerular lesions. By contrast with these findings, very slight retinal arteriolar spasm was seen in two patients, and sclerosis of the retinal arterioles was found in six patients with hypertensive vascular disease. Examination of the optic fundus therefore, was a most useful diagnostic procedure—as Wagener had clearly shown in 1933. He noted that narrowing and irregular constriction of the lumen of the arterioles was usually the first sign seen, and that the changes varied from day to day. "The variability of the narrowings and constrictions," he wrote, "and their usual tendency to rapid disappearance after the termination of the toxemia certainly suggest that they are visible signs of an angiospastic rather than an angiosclerotic lesion. The apparent permanence of some of the vascular changes indicates, however, that at some stage of the spastic process actual organic changes occur." He also pointed out that, when hypertension existed before pregnancy, any changes in the fundus were of the organic arteriolar type. Wagener assumed that the lesions which he saw in the retinal arterioles were an indication of involvement of the systemic and renal arterioles of a similar type and severity, and that the development of retinitis indicated the

* None of these patients had been treated with chlorothiazide or its derivatives.

approaching onset of organic injury to the retinal, systemic and renal arterioles which could be, in part at least, irreparable. The findings demonstrated in the kidneys of patients amply confirm the wisdom of the deductions Wagener made from his observations on the retinal arterioles.

Although most internists and obstetricians have concluded that residual renal-vascular damage may follow pre-eclampsia, this view has been repeatedly challenged by Dieckmann and his school. Dieckmann writes [*10*], "I do not believe that pre-eclampsia can last for three or more weeks, and therefore if the symptoms persist longer than that, I classify such patients as having hypertensive disease"; and "In our study of toxemia of pregnancy, we charge ourselves with the mistake if we have diagnosed pre-eclampsia–eclampsia, but at six months postpartum find evidence of vascular-renal disease or a recurrence of toxemia in a subsequent pregnancy within a three-year period." However, Dieckmann gives no evidence whatsoever for these assumptions. Moreover, his interpretations of his renal biopsy findings are also made on the basis of these same assumptions and ignore the pathologic evidence if it does not "fit in with" these assumptions [*11,12*].

The pre- and postpartum renal biopsy studies collected thus far do not appear to support Dieckmann's views, for in a few patients with the most severe pre-eclamptic lesions we have observed that, in addition to the glomerular lesions, edema and swelling of the wall of arterioles and small vessels were evident. In none of these patients were fibrosis or sclerotic vascular lesions seen in the initial biopsy specimen; yet postpartum definite vascular changes had appeared. The arterioles and small arteries were no longer swollen, but had become sclerotic, and although the glomerular edema and ischemia had disappeared, changes, distinctly vascular in nature, were observed. These were particularly prominent in the root of the glomerular tuft. As yet we have not followed the biopsied patients for a long enough period of time to determine whether or not hypertension will recur.

The term "toxemia of pregnancy" survives in widespread use today because clinicians are not successfully diagnosing the cause of the underlying disease in the individual patient. From a clinical point of view, exact diagnosis is of importance because rational prognostication and treatment depend on an accurate assessment at the height of the illness. It is the lack of diagnostic precision which has contributed materially to our present inadequate understanding of the etiology, pathogenesis and natural history of the diseases which constitute the syndrome "toxemia of pregnancy." The use of renal biopsy in these circumstances has illuminated the pathology of pre-eclampsia, clarified major clinicopathologic controversies and in the future, we predict, will elucidate the natural history of pre-eclampsia and other diseases of the kidney in pregnancy.

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Clinical Studies

Chronic Liver Disease in Young People*

Clinical Features and Course in Thirty-Three Patients

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THERE has recently been an increasing interest in chronic liver disease in young people [*1–14*]. Both Waldenström [*2*] and Kunkel et al. [*3*], have suggested that there may be a specific syndrome of chronic liver disease in young women characterized by marked hyperglobulinemia, arthritis, febrile episodes and (occasionally) hormonal disturbances. More recently Mackay and his colleagues [*7*] found lupus erythematosus (L.E.) cells in some patients with chronic active liver disease and considered these patients in a category referred to as "lupoid hepatitis." Further emphasis on the L.E. cell phenomenon in certain patients with liver disease has come from Bartholomew et al. [*11*], who described seven women with liver disease, L.E. cells and systemic manifestations.

In light of these reports we reviewed thirty-three cases of chronic liver disease in young people to ascertain whether or not any specific syndrome or separate clinical entity could be defined within this group of patients.

METHOD OF STUDY

The records of thirty-three patients with chronic liver disease who were hospitalized at the Massachusetts General Hospital between 1937 and 1959, and in whom the onset of their illness occurred prior to the age of twenty-two years, were reviewed in detail. Not included were patients with extrahepatic biliary tract obstruction, congestive heart failure, syphilis, polycystic liver disease, congenital fibrosis of the liver, Gilbert's disease or Dubin-Johnson syndrome. None of the patients whose records were reviewed had any history of alcoholism or of primary nutritional deficiency. Follow-up information was obtained in all patients up to the time of death, or if alive, up to the time of writing. Eight cases (Cases 5, 8, 11, 14, 21, 24, 25 and 29) in the present series were previously reported [*15–22*].

RESULTS

Course of Chronic Liver Disease in Young Females. There were twenty-two females with chronic liver disease. Histologic evidence of liver damage was obtained in nineteen patients and the liver was visualized by peritoneoscopy in one (Case 7). The age of onset of illness was determined by the first signs of liver disease or symptoms such as fatigue, arthralgia, edema or amenorrhea. The age of onset ranged from nine months to twenty-one years; the average age was fifteen years, with a median age of sixteen years.

A definite diagnosis of previous infectious hepatitis was difficult to substantiate but in three patients (Cases 3, 14 and 21) liver biopsies early in the course of their illness were suggestive of infectious hepatitis. Four patients (Cases 5, 9, 13 and 17) gave a history consistent with anicteric hepatitis [*23*]. No history of infectious hepatitis was obtained in the remaining sixteen patients.

In most instances, the young females had a progressive course with intermittent or low grade jaundice, splenomegaly, edema, ascites and esophageal varices. (Table 1.) The majority of the patients had menstrual disturbances; over two-thirds of the group had primary or secondary amenorrhea, whereas two patients had irregular or scanty menses at the beginning of their illness. One patient (Case 5) became pregnant but the pregnancy was terminated in the

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TABLE 1

MAJOR CLINICAL FEATURES OF THIRTY-THREE PATIENTS WITH CHRONIC LIVER DISEASE UNDER AGE TWENTY-TWO

Case No.	M.G.H. No.	Age at Onset (yr.)	Sex	Duration (yr.)	Previous Hepatitis	Jaundice	Splenomegaly	Esophageal Varices	Ascites	Peripheral Edema	Spider Angiomas	Striae	Acne	Itching	Arthralgia	Febrile Episodes	Menses*	Ulcerative Colitis
1	680828	13	F	7†	0	+	+	+	+	+	+	+	+	0	+	+	A	0
2	1036229	21	F	1½	0	+	0	0	0	0	0	+	+	+	+	+	A	0
3	498845	16	F	6†	Possible	+	+	0	+	+	0	0	+	0	0	+	A	+
4	299174	19	F	2†	0	0	+	+	+	+	0	0	0	0	0	+	IRR	0
5	213526	14	F	6†	Possible	+	+	0	+	+	+	0	+	+	+	+	‡	+
6	373960	16	F	½†	0	+	+	+	+	+	+	+	+	+	0	+	A	0
7	443061	12	F	3†	0	+	+	0	0	+	+	0	+	0	0	0	A	0
8	221008	17	F	1½†	0	+	+	0	+	+	0	0	0	0	+	+	R	+
9	752611	20	F	2†	Possible	+	+	0	+	+	+	0	0	0	0	0	A	0
10	798643	10	F	7†	0	+	+	+	+	+	+	+	+	0	0	+	A	0
11	649830	20	F	2†	0	+	+	+	+	+	+	0	0	0	+	+	A	+
12	243975	17	F	1½†	0	+	+	...	0	0	+	0	0	+	0	+	A	0
13	639709	10	F	4½†	Possible	+	+	+	0	0	+	0	+	0	0	+	A	0
14	506827	19	F	3½†	Possible	+	+	+	+	+	+	0	+	0	+	+	A	0
15	475677	16	F	...†	0	+	+	0	0	+	0	0	0	0	0	+	A	0
16	494163	17	F	4†	0	+	+	0	+	0	0	+	+	0	0	+	A	0
17	691526	16	F	4†	Possible	+	+	+	+	+	+	0	0	0	0	+	IRR	0
18	1040599	13	F	¾†	0	+	+	0	+	+	+	+	+	+	+	+	A	0
19	738727	14	F	8	0	+	+	+	0	0	+	0	+	+	+	+	A	0
20	862887	11	F	6†	0	+	+	+	+	+	+	+	+	0	0	0	R	+
21	988381	¾	F	1½†	Possible	+	+	0	+	+	0	+	0	0	0	+	...	0
22	1046717	16	F	3†	0	+	+	+	+	+	0	0	+	+	0	+	A	0
23	859342	14	M	6	+	+	+	+	+	+	+	0	0	0	0	+	...	0
24	100887	11	M	½†	0	+	+	+	+	0	0	0	0	0	0	+	...	0
25	519416	7	M	6†	Possible	+	+	0	+	+	0	0	0	+	+	0	...	0
26	738728	12	M	10	0	0	+	0	0	0	+	0	+	0	+	+	...	+
27	790316	2	M	16†	0	+	+	+	0	+	+	0	0	0	0	+	...	0
28	945239	8	M	5	+	+	+	+	+	+	+	0	0	0	0	+	...	0
29	446472	14	M	4†	0	+	0	+	+	+	+	0	+	+	0	+	...	+
30	982666	21	M	4	0	0	+	+	0	0	0	0	0	0	0	0	...	0
31	941136	15	M	2†	0	+	+	+	0	0	+	+	+	0	0	+	...	0
32	412804	14	M	5†	Possible	+	+	...	+	+	0	0	0	0	+	0	...	0
33	461016	13	M	6†	0	Probable	+	+	+	0	0	0	0	0	0	0	...	0

* R = Regular menses at time of admission to hospital, no subsequent information recorded.
IRR = Irregular menses at time of admission to hospital, no subsequent information recorded.
A = Amenorrhea during course of the disease.

† Died.

‡ Regular menses, followed by pregnancy and therapeutic abortion, no subsequent information recorded.

TABLE II

LABORATORY FINDINGS IN THIRTY-THREE PATIENTS WITH CHRONIC LIVER DISEASE UNDER AGE TWENTY-TWO

Case No.	Serum Bilirubin* (total) (mg./100 ml.)	Serum Globulin* (gm./100 ml.)	Serum Alkaline Phosphatase* (Bodansky units)	Eosinophils* (%)	Cephalin Flocculation	Liver Histology Available	Liver Weight† (gm.)
1	1.2- 4.4	2.8- 5.7	2.6–11.9	0- 5	4+	+	1,100
2	2.9- 9.8	3.8- 6.7	5.9- 6.9	1–10	4+	+	
3	nl.‡–12.2	3.3- 6.9	6.4	0- 9	4+	+	850
4	nl.–...	2.7	5.4	1	...	+	
5	1.2–32.8	3.3- 6.0	8.1- 8.4	3	4+	+	900
6	3.5- 6.8	7.5- 8.5	5.1	0	3+	+	1,850
7	2.2- 4.4	3.7- 4.3	15.8–22.6	1- 4	4+	0§	
8	4.1- 5.1	4.0	...	0–48	...	+	2,500
9	3.6	3.9	5.9	4	4+	0	
10	0.8- 9.8	3.1- 5.1	6.5- 7.0	0- 7	4+	+	630
11	6.6- 9.8	1.8- 3.7	...	3	4+	+	1,200
12	2.0–10.1	6.3- 8.5	3.0	0- 4	4+	0	
13	3.2–16.0	3.5- 6.2	15.8–16.7	0- 5	4+	+	800
14	1.9- 6.6	6.8–11.2	3.8–10.0	0- 8	4+	+	1,900
15	1.5- 2.7	3.5- 5.6	8.7–14.7	1	4+	+	
16	2.4- 6.8	4.0- 4.5	13.7	0- 8	4+	+	
17	2.8–19.5	4.5- 5.7	10.1–25.5	3–12	4+	+	
18	6.6–22.4	3.1- 4.8	3.6–12.5	2	4+	+	1,010
19	1.0- 3.4	5.0- 7.6	9.7–21.2	2- 7	4+	+	
20	0.8–18.0	2.8- 5.3	6.4–13.6	1- 4	4+	+	1,250
21	2.2–17.9	1.9- 3.3	10.0–81.0	0- 4	3+	+	610
22	7.5–16.0	3.9- 8.2	11.1	1	4+	+	1,200
23	0.8- 6.3	1.1- 3.0	5.2	0- 9	3+	+	
24	3.4–13.3	3.2	...	2	...	+	925
25	1.1- 2.8	3.1- 3.7	5.9–11.3	0- 8	4+	+	1,100
26	nl.	3.5- 4.7	4.0–15.3	2- 5	3+	+	
27	2.0–24.3	4.0- 5.1	6.5–17.3	2- 4	3+	+	
28	0.9- 3.8	2.6- 4.2	7.5–40.3	3–27	3+	+	
29	nl.- 4.3	2.6- 3.5	3.3–19.8	1- 6	3+	+	950
30	nl.	1.9	...	2- 7	3+	+	
31	2.9- 8.7	3.7- 6.0	6.4- 9.8	1- 8	4+	+	1,100
32	nl.—...	3.0- 4.6	...	1	4+	+	
33	nl.-...	3.1	...	0	...	+	

* Figures represent lowest and highest values recorded.
† Liver weight not corrected for age.
‡ nl. = Normal value of total bilirubin (up to 0.7 mg. per 100 ml.).
§ Had a peritoneoscopy but no liver biopsy.

seventh month because of severe liver disease. Eight patients (36 per cent) had pale non-abdominal striae and fourteen (63 per cent) had acne. Arthralgia was present in eight patients (36 per cent). There were recurrent febrile episodes in nineteen patients. Ulcerative colitis, present in five patients, was confirmed at autopsy. Colitis developed in four of these five patients *after* the onset of liver disease, whereas in the fifth patient (Case 11) colitis was present two years *before* any symptoms of liver disease. Two patients had other systemic manifestations. At autopsy one (Case 3) was found to have myocarditis, chronic glomerulonephritis and some degenerative lesions in the central nervous system; the other (Case 19) had pericarditis and a pericardial biopsy showed a granulomatous process suggestive of a rheumatoid nodule.

Laboratory data (Table II) showed progressive liver dysfunction with abnormal flocculation tests, low prothrombin time, increased bromsulfalein retention and low serum albumin levels (less than 3.5 gm. per 100 ml. of serum). The serum alkaline phosphatase was slightly

TABLE III
RELATIVE INCIDENCE OF MAJOR CLINICAL FEATURES IN YOUNG PEOPLE WITH CHRONIC LIVER DISEASE

Clinical Features	Females (%)	Males (%)
Jaundice	95	82
Splenomegaly	95	91
Esophageal varices	50	80
Ascites	73	64
Peripheral edema	77	54
Spider angiomas	64	54
Striae	36	9
Acne	64	27
Itching	32	18
Arthralgia	36	27
Febrile episodes	86	54
Total no. patients	22	11

elevated in most patients. In one patient (Case 21) the alkaline phosphatase was as high as 81 Bodansky units; however, at autopsy this patient had a small hepatoma (1 cm. in diameter) which may have contributed to the high serum enzyme level. Peripheral blood smears showed eosinophils in excess of 5 per cent in one-third of the patients at some time during their disease. One patient (Case 8) had eosinophils as high as 41 per cent during the course of the illness. Albuminuria, without signs of urinary infection, was present terminally in three patients (Cases 8, 11 and 18). Smears of the peripheral blood for L.E. cells were prepared and examined in four patients. In one patient (Case 22) one of six L.E. preparations was positive; in another (Case 2), a probable L.E. cell was seen in a single preparation. In the remaining two patients (Cases 19 and 21) several smears were negative for L.E. cells. One of the striking laboratory findings was the elevation of serum globulin levels. The mean of the highest serum globulin levels was 5.8 $\pm$ 2 gm. per 100 ml. of serum. The second globulin levels were followed in nineteen patients during the course of their illness. As the disease progressed the globulin values fell more than 1 gm. per 100 ml. of serum in thirteen of the nineteen patients. It did not vary in five patients and increased in only one (Case 3). In nine patients with elevated serum globulin levels the gamma globulins were checked electrophoretically and were found to be increased in eight.

Corticosteroids were administered in varying dosages for periods ranging from two weeks to twenty-two months in five patients (Cases 2, 17, 18, 20 and 21) and resulted in marked clinical improvement in only one (Case 2). There was no improvement in the other four patients except for some decrease in the serum globulin levels. Splenorenal shunts were performed for upper gastrointestinal bleeding in two patients (Cases 10 and 19) and for hypersplenism in one (Case 1). One patient (Case 4) had an omentopexy, another (Case 22) ligation of esophageal varices for gastrointestinal hemorrhage. Except in one instance (Case 19) the surgical procedures did not seem to influence the over-all course of the illness. A total colectomy was performed in a patient (Case 3) with ulcerative colitis and liver disease without any improvement of the liver disease.

The prognosis in the female group was poor. To date, twenty of the twenty-two patients have died. The terminal episode was documented in seventeen of the patients; all died in hepatic failure, gastrointestinal bleeding occurring in seven (Cases 1, 8, 10, 14, 18, 21 and 22). The average duration of the disease in the patients who died was three and a half years, with a range of six months to seven years. The median duration was three years. Two girls (Cases 2 and 19) still alive at the time of this writing have had their disease for two and eight years, respectively.

Course of Chronic Liver Disease in Young Males. There were eleven males with histologically proved chronic liver disease. The average age at the onset of the disease was eleven years and ranged from two to twenty-one years. There was a history of antecedent infectious hepatitis in two patients (Cases 23 and 28) and a possibility of anicteric hepatitis in two others (Cases 25 and 32). The clinical picture (Table I) was, as a rule, similar to that observed in the female patients except that esophageal varices were more frequent (80 per cent) and recurrent febrile episodes, acne and striae were less frequent. (Table III.)

The evolution of the disease was somewhat longer and the prognosis slightly better. To date, of the eleven males seven have died, and in these the duration of the disease varied from five months to sixteen years. The average and median duration was about the same, five years. Two of the eleven males had ulcerative colitis, one (Case 29) before the onset of the liver disease and the other (Case 26) afterward.

In all patients, results of liver function tests were abnormal. (Table II.) In nine cases the serum albumin level was below 3.5 gm. per 100 ml. and the serum globulin levels higher than 3 gm. per 100 ml. (average 3.9 ± 1.2) at some time during their illness. No L.E. cell preparations were made and no serum protein electrophoretic studies were performed. Eosinophils above 5 per cent were present in five patients and were as high as 27 per cent in one (Case 28). Albuminuria was present in two patients (Cases 28 and 29).

Two patients (Cases 25 and 31) were treated with steroids (for three weeks and several months, respectively) without any clinical improvement. Another patient (Case 26) did well for four years without steroid therapy, but because of an exacerbation of his ulcerative colitis he was given corticosteroids. This treatment was started two and a half years ago and has been maintained to date. Splenorenal shunts were performed for upper gastrointestinal bleeding in two cases (Cases 23 and 31) but gastrointestinal bleeding recurred in both. In one patient (Case 28) a splenorenal shunt was performed for hypersplenism and portal hypertension, with good results. Omentopexy was performed in one patient (Case 24) and splenectomy in another (Case 27), but both died with massive hematemesis.

ADDITIONAL DATA

Pathologic Aspects. Liver tissue was obtained by biopsy or at autopsy in nineteen of the twenty-two females and in all of the male patients. In twelve cases, liver tissue was available at different times during the disease. All histologic slides were reviewed by us except those in Case 16, as material was no longer available.

Increased fibrosis was apparent in all histologic specimens and derangements of lobular architecture and increased bile duct proliferation were present in most. Inflammatory exudates, primarily in the connective tissue bands, consisted largely of lymphocytes and plasma cells. These were present in all specimens, but were markedly increased in those of eight female patients (Cases 2, 6, 8, 10, 14, 18, 19 and 22) and three male patients (Cases 31, 32 and 33). Only a few liver sections were subjected to Gomori's silver impregnation, so that estimation of reticulum collapse was not attempted. Other than bile pigments, no pigments were detected in hepatic or Kupffer cells. Councilman bodies were found in six cases and binucleated or multinucleated cells in seven. Mild fatty infiltration was noted terminally in twelve patients; pronounced fatty infiltration was present in only two (Cases 6 and 8).

The livers, when examined at autopsy, were pale with large fibrotic bands and regenerating nodules of varying size. All were considered to be postnecrotic in appearance. An adenoma of the liver was present in one patient (Case 14) and a small hepatoma (1 cm. in diameter) in another (Case 21). The usual absence of Laennec's cirrhosis in young people with chronic liver disease has also been noted by other investigators [*4,5,8,9*].

Liver weight was recorded in seventeen cases. When these values were corrected for age [*24,25*], the liver weight was increased in four, normal in seven and decreased in six. There was no definite correlation between the liver weight, age at onset of illness, duration of the disease or previous hepatitis.

Protein Disturbances. At the Massachusetts General Hospital the serum total proteins are determined by the Biuret procedure [*26*] and the serum albumin likewise, after separation by the Howe method [*27*]. The serum globulins are calculated by the difference between the two values and represent only the beta and gamma globulins; the alpha fraction is included in the albumin value. Normal serum globulin levels range between 1.5 and 3 gm. per 100 ml. If one considers the highest recorded serum globulin levels in the patients of this series, the females had a mean serum globulin level of 5.8 ± 2 gm. per 100 ml. (range 2.7 to 11.2) and the males a mean of 3.9 ± 1.2 gm. per 100 ml. (range 1.9 to 6). (Fig. 1.) The standard error of the difference between the means is 0.56. From these data, the observed differences in the mean globulin values of the females as compared with the males is highly significant ($p < 0.003$). In this connection it is pertinent that serum globulin levels of over 6.6 gm. per 600 ml. of serum were found only in the young female patients. In calculating the mean of the highest globulin levels recorded for the twenty-one female patients of Bearn, Kunkel and Slater [*5*] under age twenty-two, we obtained a value of 6.2 ± 1.8 gm. per 100 ml. of serum (range 4 to 9.4 gm per 100 ml.). This is comparable to the mean value in the present series. In five young patients with chronic "lupoid" hepatitis, Ogryzlo et al. [*28*] found an average serum globulin level

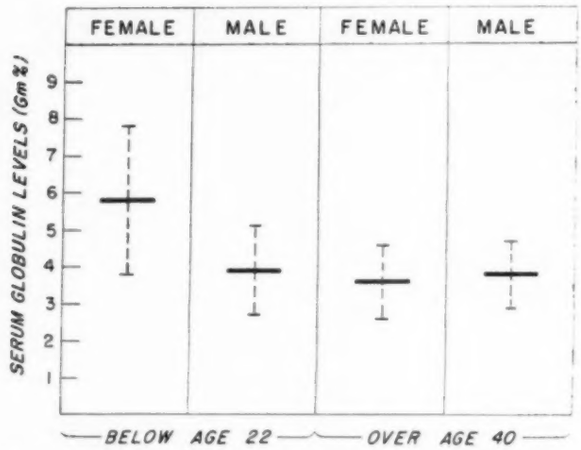


FIG. 1. Mean values of highest recorded serum globulin levels in patients with chronic liver disease under the age of twenty-two and over the age of forty. Horizontal lines represent the mean values and the vertical lines the standard deviation.

TABLE IV
OCCURRENCE OF ARTHRALGIA AS RECORDED IN ALCOHOLIC AND NON-ALCOHOLIC PATIENTS WITH CHRONIC LIVER DISEASE OVER AGE FORTY

Sex	Patients (no.)	Arthralgia		Average Age (yr.)	Age Range (yr.)
		No.	%		
Alcoholic Patients with Chronic Liver Disease					
M	50	6	12	69	61–75
F	25	6	24	55	44–84
Non-alcoholic Patients with Chronic Liver Disease					
M	28	2	7	66	60–73
F	28	9	32	59	43–71

of 7.45 gm. per 100 ml. (range 4 to 8.6 gm. per 100 ml.).

For comparison, we reviewed the records of 143 patients over forty years of age with histologic evidence of Laennec's or postnecrotic cirrhosis and noted the highest recorded serum globulin values. The mean of the globulin levels in this group was 3.7 ± 1 gm. per 100 ml. of serum (range 1.2 to 6.5 gm. per 100 ml.), which is somewhat lower than the average usually reported. Patek [*29*] observed a mean value of 4.1 gm. per 100 ml. of serum in forty-five cases of postnecrotic cirrhosis, whereas in forty patients with portal cirrhosis Ogryzlo et al. [*28*] found an average of 3.93 gm. per 100 ml. Armas-Cruz [*30*] observed that 56 per cent of his cirrhotic patients had a globulin level above 4 gm. per 100 ml. Occasional instances of hyperglobulinemia as high as 9.9 gm. per 100 ml. of serum have been reported in cirrhotic patients of different age groups [*31*]. In the 143 cirrhotic patients above age forty whose records were reviewed by us there was no difference in the levels of the mean globulin values between males and females. There were eighty-seven males with a mean serum globulin of 3.8 ± 0.9 gm. per 100 ml. (range 1 to 6.5 gm. per 100 ml.) and fifty-six females with a mean level of 3.6 ± 1 gm. per 100 ml. (range 1.2 to 6.6 gm. per 100 ml.). The standard error of the difference between the means was 0.17 and the difference was not significant. The highest serum globulin level recorded in this entire age group was 6.6 gm. per 100 ml. There was no difference in these patients when they were divided into those with Laennec's cirrhosis and those with postnecrotic cirrhosis. The patients with Laennec's cirrhosis (and a history of chronic alcoholism) had a mean serum globulin value of 3.6 ± 0.9 gm. per 100 ml. and those with postnecrotic cirrhosis (and no history of chronic alcoholism) had a mean level of 3.8 ± 1 gm. per 100 ml.

In view of the high serum globulin levels observed in the young females with chronic liver disease, it seemed possible that normal young females might also have higher serum globulin levels than either young males or older subjects. According to Oberman et al. [*32*] adult levels of serum globulin are reached at seven to eleven months of age, although Trevorrow and associates [*33*] believe they are not reached until four years of age. We determined the serum globulin levels in twenty-one student nurses under the age of twenty and found a mean value of 1.9 ± 0.2 gm. per 100 ml. (range 1.4 to 2.7). These results confirm the impression that serum globulin levels in normal young females do not differ from the accepted normal values. It is also pertinent that in young patients with other forms of chronic liver disease not included in this study (e.g., secondary biliary cirrhosis and cardiac cirrhosis) no exceptionally high serum globulin values were observed.

Arthralgia. One-third of the females (36 per cent) and one-fifth of the males (18 per cent) complained of arthralgia at some time during their illness. In contrast to arthralgia, the

incidence of arthritis could not be evaluated from available data. Five of the patients had joint pains associated with clinical jaundice but in none was the serum bilirubin higher than 4.4 mg. per 100 ml. at the time of the joint symptoms. The patients with rheumatic disease studied by Hench [*34*] had relief of their joint pains when the serum bilirubin level was above 8 mg. per 100 ml. We also examined the charts of 131 patients above the age of forty with cirrhosis and recorded the incidence of arthralgia. (Table IV.) In this group the incidence of joint symptoms is greater in the female patients. Furthermore, the incidence of arthralgia is higher in the non-alcoholic female patients with chronic liver disease (postnecrotic cirrhosis) than in the alcoholic group (Laennec's cirrhosis).

Ulcerative Colitis. Seven patients, five females and two males, had both chronic liver disease and ulcerative colitis. In five the liver disease appeared to precede the colitis. Gray et al. [*35*] reported eight cases of "hepatitis, colitis and lupus manifestations" in two of which the hepatitis antedated the colitis. The frequency of ulcerative colitis in young patients with chronic liver disease appears to be too great to be explained purely on the basis of coincidence. Previous investigators [*36–38*] have noted that cirrhosis may follow and perhaps represent a complication of ulcerative colitis. On the other hand, Olhagen [*39*] observed that in six of ten patients with ulcerative colitis and cirrhosis, the cirrhosis appeared first.

Above age forty, the occurrence of ulcerative colitis and chronic liver disease in the same patient is uncommon. Of the 143 patients with cirrhosis over the age of forty whose records were reviewed, not one had both cirrhosis and colitis.

COMMENTS

It has been suggested by a number of authors [*2,5*] that some young patients with chronic liver disease, especially females under age thirty-five, have a type of cirrhosis with distinct clinical features. These patients have been considered in a separate clinical category when their manifestations include amenorrhea, acne, abdominal striae, febrile episodes, arthralgia, hyperglobulinemia and eosinophilia. In the present series of thirty-three young patients with chronic liver disease, which included twenty-two females and eleven males, no consistent clinical or laboratory features were found to permit a separation of any of the patients into a single clinical entity or syndrome. The clinical features and course of these thirty-three patients were quite variable. In some the disease was fulminating; in others it progressed more slowly. No significant correlation was found between the severity of the clinical manifestations and abnormal laboratory findings such as hyperglobulinemia and eosinophilia. (Tables I and II.)

Febrile episodes occurred in nineteen of the twenty-two female patients (86 per cent) and in six of the eleven male patients (54 per cent). However, it should be recalled that fever and febrile episodes occur in various types of cirrhosis and are not unique to young patients with chronic liver disease. King [*40*] for example, noted that only fourteen of eighty-one cirrhotic patients had normal temperatures, and Ratnoff and Patek [*41*] found 40 per cent of their patients with postnecrotic cirrhosis to have a febrile course.

The female patients differed from the male patients in that they had significantly higher serum globulin levels. The reason for this is unexplained, especially since serum globulin levels in a group of healthy young girls of a comparable age were entirely within the normal range. Menstrual disturbances were found in twenty of the twenty-two females (90 per cent) but these are not unusual in older, premenopausal women with cirrhosis, either of the Laennec or postnecrotic type [*42–44*]. In view of the incidence of amenorrhea, acne and striae in our female patients, it seems quite likely, as suggested also by others [*5,45*], that hormonal factors are important in chronic liver disease and that the course of the illness may be significantly influenced by the endocrine environment. Support for such a concept is obtained from the observations of Bearn, Kunkel and Slater [*5*]. These authors noted that in some of their female patients with chronic liver disease the administration of estrogens was followed by elevations in serum bilirubin levels.

Although the cause of chronic liver disease of the postnecrotic type is unknown, viral hepatitis is frequently implicated as an etiologic agent. Klatskin [*46*] is of the opinion that a history of previous anicteric viral hepatitis can frequently be elicited in patients with postnecrotic cirrhosis. It is difficult in the patients of our series to be certain whether hepatitis had occurred prior to the diagnosis of their chronic liver disease. In the female patients there was no definite history of previous icteric viral hepatitis, although anicteric

hepatitis may have been present in four patients (Cases 5, 9, 13 and 17). In the male patients two (Cases 23 and 28) had a history of previous icteric viral hepatitis and this diagnosis was a possibility in two other patients (Cases 25 and 32). These findings are comparable to those of Craig et al. [*4*] who considered viral hepatitis a possible factor in eight of twenty-one children with cirrhosis. In contrast, Ruggieri et al. [*9*] concluded that viral hepatitis was the most frequent etiologic agent in twenty-seven cases of juvenile cirrhosis reviewed by them.

The presence of L.E. cells in the peripheral blood of one and possibly two of the female patients raises the question of the relationship of their illness to disseminated lupus erythematosus (D.L.E.) and to "lupoid hepatitis" [*7*]. Harvey et al. [*47*] found only three cases of cirrhosis in 138 patients with D.L.E., whereas Kofman, Johnson and Zimmerman [*48*] found no evidence of cirrhosis in twenty-five cases. Bartholomew [*11*], on the other hand, described seven women with a clinical picture suggestive of D.L.E. and liver disease. Mackay and his colleagues [*7,13*] have introduced the term "lupoid hepatitis" for patients with chronic active hepatitis and a positive reaction to the L.E. cell test. However, except for the presence of L.E. cells in the peripheral blood [*49–53*], these patients cannot be distinguished clinically from others with chronic liver disease. Furthermore, in several of the fourteen cases reported by Mackay [*13*], the L.E. phenomenon was not readily demonstrated. In one patient only one of twenty-four L.E. cell test results was positive; in another, only one of eleven test results was positive.

It is pertinent to consider whether the finding of a positive L.E. test result in these patients is sufficient to place them into a separate clinical category. The L.E. cell phenomenon is known to be due to circulating antinuclear antibodies which react with the nuclear material (deoxyribonucleohistone) of the leukocytes [*54*]. Current evidence indicates that the antinuclear antibodies are byproducts of an altered or abnormal immunologic system. Although these antibodies occur in the great majority of patients with D.L.E. [*55*], they also occur in other diseases. L.E. cells have been found, for example, in various allergic states, patients treated with penicillin [*56*] or with hydralazine [*57,58*], and in some instances of pernicious anemia [*59*], acute hemolytic anemia, amyloidosis [*60*] and moniliasis [*61*]. These observations raise doubts as to the specificity of the L.E. phenomenon and suggest that it may only be a reflection of an allergic process, perhaps of the autoimmune type. In this connection it should be mentioned that whether D.L.E. is really one disease entity still remains to be determined [*62,63*].

The separation of patients with chronic active liver disease into those with and without a positive reaction to the L.E. cell test would seem desirable if different etiologic factors were involved or if these patients manifested a different clinical course or response to therapy. Certainly the prognosis was poor in the majority of the patients of our series. Similarly, in the patients reviewed by Mackay [*13*] six were under age twenty-two and of these, four died. In regard to therapy, seven of our patients, five females and two males, were treated with corticosteroids for periods ranging from two weeks to twenty-two months. Significant clinical improvement occurred only in one (Case 2). In Mackay's series there was no clinical improvement in three of five patients receiving corticosteroid therapy [*13*]. On the other hand, Bearn, Kunkel and Slater [*5*] found corticosteroids of value in a number of their young patients with chronic liver disease. Although clinical improvement frequently was not maintained when the treatment was stopped, they have suggested the use of corticosteroid therapy in such patients.

The hypothesis has been advanced that chronic active hepatitis or chronic liver disease, especially in young people, may involve an autoimmune process [*63,64*]. In this concept it is suggested that protein release from damaged liver cells is followed by the production of autoantibodies. Subsequent antigen-antibody interactions [*64*] then presumably lead to further hepatic damage. Gajdusek [*65*] has found an increase of antibodies to liver antigens in the serums of patients with chronic active hepatitis, both in those with and without L.E. cells. Elevated antibody titers were found in 78 per cent of his patients with chronic active hepatitis and in 75 per cent of those with "lupoid hepatitis." In a recent report, Behar and Tal [*66*] have described necrosis of liver parenchyma in some guinea pigs and hamsters after the injection of an homologous liver homogenate together with Freund's adjuvant. Their findings would support the concept that some forms of chronic liver disease may be related to autoimmune processes.

In our opinion the separation of patients with chronic liver disease into two clinical

groups solely on the basis of a positive or negative reaction to the L.E. cell test is not justifiable at the present time. Indeed, the incidence of patients with chronic liver disease and a positive reaction to the L.E. cell test may be related to the intensity of the search for L.E. cells or to the sensitivity of the method for demonstrating the antinuclear antibodies. Furthermore, the L.E. phenomenon may only be another reflection of an allergic or autoimmune process present in many forms of chronic active liver disease.

The high incidence of ulcerative colitis in our patients is noteworthy. Although the etiology of ulcerative colitis is still unknown, alterations in circulating antibodies have recently been described in this disease. Broberger and Perlmann [*67*] have shown that most of the serums of thirty children with ulcerative colitis contained a precipitating and hemagglutination factor reacting with a constituent of human colonic tissue. The precipitating factor behaved electrophoretically as a gamma globulin. At this time one can only speculate whether ulcerative colitis occurring in patients with chronic liver disease is also part of an autoimmune process. It is of interest that in the 113 patients with fatal acute hepatitis studied by Lucké [*68*], seventeen had an inflammatory and twenty-six a non-inflammatory type of edema of the small and large intestine. It is possible, therefore, that acute and chronic liver disease may set the stage for subsequent intestinal involvement.

SUMMARY AND CONCLUSIONS

The clinical features and course of twenty-two female and eleven male patients with chronic liver disease, manifest before age twenty-two, have been reviewed. The clinical features were similar in both groups, except that recurrent febrile episodes, acne and striae were more prominent in the female patients and esophageal varices more common in the male patients. Arthralgia was noted in 36 per cent of the females and in 27 per cent of the male patients. Ulcerative colitis was present in seven patients; in five of these it appeared after the onset of the liver disease.

In general the prognosis was poor. Twenty of the twenty-two female patients and seven of the eleven male patients have died. The average duration of the disease in those who died was three and a half years in the female patients and five and a half years in the male patients.

Liver function was markedly impaired in all patients. The serum globulin levels were elevated, but were significantly higher in the young female patients as compared either to the young male patients or to older patients with chronic liver disease. L.E. cell tests were performed in four patients and results appeared to be positive in two. The histologic diagnosis of the liver disease in thirty of the patients was postnecrotic cirrhosis.

Viral hepatitis appears to have occurred in some of these patients. The concept that the hepatitis virus or other agents may have caused the chronic liver disease by autoimmune mechanisms is discussed. The clinical course of the thirty-three patients did not differ from that of published cases of chronic liver disease with L.E. cells, referred to by some as "lupoid hepatitis."

The L.E. cells probably are a manifestation of immune or allergic processes. Rather than implying a separate etiology, the presence of L.E. cells in some patients with chronic liver disease may only be a reflection of the intensity of the search for these cells or the level of the L.E. factor.

In the present series of thirty-three young patients with chronic liver disease, we have found no consistent clinical or laboratory features that warrant a definite separation of any of these cases into a clinical entity.

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Fatty Liver Presenting as Obstructive Jaundice*

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An increase in liver fat detected histologically or by chemical analysis has been termed fatty liver, fatty metamorphosis of the liver or hepatic steatosis. The normal liver contains 5 per cent fat (wet weight), while in pathologic states the amount of fat may exceed 40 per cent [*1*]. Increased amounts of fat in the liver have been noted in many conditions, including chronic alcohol usage, nutritional deficiencies, severe anemia, diabetes mellitus, chloroform or phosphorus ingestion, tuberculosis and various xanthomatoses [*2*]. In the majority of cases in which the pathologist describes fatty liver, the patient does not present clinical symptoms or detectable derangement of liver function. In some cases, however, fatty liver may be the only histologic finding associated with jaundice and biochemical alterations.

During the past four years we have observed a group of patients on the Medical Service of the New York V. A. Hospital characterized by excessive alcohol intake, jaundice, hepatomegaly, and biochemical tests suggestive of biliary tract obstruction. Percutaneous biopsy specimens of liver revealed pathologic amounts of fat in the liver, intrahepatic cholestasis and little or no evidence of cirrhosis. This paper will describe five of these cases.

CASE REPORTS

CASE I. A. C., a thirty-eight year old white man, was admitted to this hospital for the second time on June 6, 1959, because of jaundice. He was first admitted six weeks previously because of jaundice which resolved without specific treatment. The diagnosis of cholangiolitic hepatitis was suspected but liver biopsy was not performed. One week prior to his second hospital entry he noted anorexia, dark urine, light colored stools and tenderness in the right upper quadrant. He had a history of moderately heavy alcoholic intake for many years and a very large intake just before his first admission to the hospital. He denied drinking after discharge. There had been no contact with hepatotoxic agents, no contact with jaundiced persons.

Physical examination revealed a well developed, obese white man in no apparent distress. The skin was deeply jaundiced. Both parotid glands were enlarged. The liver edge was firm, slightly tender, and approximately 8 cm. below the right costal margin. Generalized coarse tremors of the extremities were present.

The urine contained bile and a normal concentration of urobilinogen (1:20 dilution). Examination of the blood revealed a hemoglobin of 14.2 gm. per cent, a white blood cell count of 6,700 per cu. mm. Biochemical studies suggested obstructive jaundice. (Table I.) A liver biopsy performed nine days after admission revealed prominent fat vacuoles in the liver cords and bile stasis. (Fig. 1.) The subsequent clinical course was uneventful. The liver edge receded to the right costal margin and the abnormal laboratory values returned to normal on bed rest and adequate diet. An oral cholecystogram performed three weeks after admission revealed a well visualized gallbladder without evidence of biliary calculi.

CASE II. T. H., a forty year old white man, was admitted to the hospital on November 1, 1955, because of jaundice. Two weeks prior to admission he had first noted dark brown urine, light colored stools and anorexia. Several days later the skin was noted to be yellow. The patient had been a heavy drinker of alcoholic beverages for many years. During the month preceding admission he had increased his alcoholic intake and during the same period lost 20 pounds. There was no history of exposure to hepatotoxins, contact with jaundiced persons or recent injections.

Physical examination showed a well developed, thin, white man with icterus of the skin and sclera. Abdominal examination revealed a smooth, nontender liver edge which extended 6 cm. below the right costal margin.

The urine gave a positive test for bile. Examination of the blood revealed a hemoglobin of 10.8 gm. per cent, and a white blood cell count of 6,700 per cu.

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TABLE I

LABORATORY FINDINGS IN PATIENTS WITH FATTY METAMORPHOSIS OF THE LIVER ASSOCIATED WITH JAUNDICE

Case No.	Hospital Days	Serum Bilirubin (mg./100 cc.)	Serum Alkaline Phosphatase (King-Armstrong units)	Serum Cholesterol (mg./100 cc.)	Cephalin-Cholesterol Flocculation	Thymol Turbidity (units)	Brom-sulphalein Retention (%)	Pro-thrombin (seconds)	Serum Albumin (gm. %)	Serum Globulin (gm. %)
I	2	19.8	40	...	...	6.0	...	13	4.8	1.9
	6	...	...	640	...	...	...	...	...	...
	12	6.9	34	638	Negative	3.4	...	12	4.8	1.9
	14	2.2	29	308	Negative	1.3	...	...	5.4	2.8
	30	0.8	26	282	...	2.6	...	13	...	...
	47	0.8	16	254	Negative	...	...	13	5.3	2.5
II	2	...	64	1,220	Negative	1.6	...	...	2.9	2.6
	7	4.4	...	930	...	...	...	...	...	...
	14	3.6	25	616	...	...	5	...	...	...
	21	0.5	16	460	Negative	...	...	14	3.7	2.7
	36	0.6	10	237	...	...	...	...	...	...
III	4	29.0	92	810	Negative	...	...	...	3.2	2.9
	7	33.0	...	...	Negative	0.6	...	...	...	...
	18	14.6	36	422	Negative	...	...	15	...	...
	26	7.9	23	...	...	...	...	...	...	...
	40	3.8	16.5	...	Negative	...	...	...	...	...
	54	1.1	14	214	Negative	...	...	...	4.1	2.5
IV	3	26.6	47.6	770	2+	...	...	...	3.5	2.5
	6	...	56	722	Negative	3.9	...	15	...	...
	12	21.2	26	438	2+	...	...	14	...	...
	20	16.0	41	383	Negative	...	...	...	3.9	2.6
	31	0.2	37	357	2+	...	...	...	...	...
	50	...	12	240	Negative	...	8	12	...	...
V	4	24.4	32	596	Negative	3.1	...	14	5.1	3.2
	18	12.9	17.3	475	Negative	3.4	...	...	...	...
	25	6.6	23	498	1+	3.6	...	13	4.7	3.1
	54	1.0	9.4	250	Negative	3.4	...	...	...	...

mm. Biochemical studies suggested obstructive jaundice. (Table I.)

Management consisted of bed rest and a balanced diet with vitamin supplements. Liver biopsy performed after subsidence of jaundice revealed moderate fatty metamorphosis and bile stasis. Jaundice regressed slowly and the liver decreased markedly in size over the course of one month of hospitalization. X-ray examination of the upper gastrointestinal tract and oral cholecystography performed at this time were reported as being within normal limits. At the time of hospital discharge, on the thirty-fifth hospital day, he had gained 22 pounds, the liver edge was beneath the right costal margin and liver function test results were all within normal limits.

CASE III. W. F., a fifty-four year old white man, entered the hospital on August 1, 1958, because of anorexia, pedal edema and scleral icterus of ten days' duration. The patient admitted to drinking a minimum of 1 pint of whiskey and 10 pints of beer daily for many years. He stated that he had been drinking "more than usual" for several weeks prior to his admission and that his food intake had decreased markedly during the same period. He denied any previous episodes of jaundice, fever or myalgia. There was no history of contact with hepatotoxic agents, recent transfusions or injections within the six months preceding hospital entry.

Physical examination revealed a well developed, poorly nourished, deeply jaundiced white man. The liver edge was firm and non-tender and was palpated

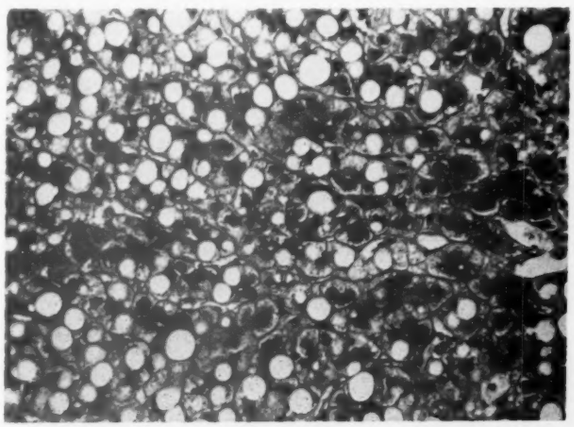


FIG. 1. Case I. Photomicrograph of liver biopsy specimen obtained on ninth hospital day, revealing prominent fat vacuoles in the liver cords and bile stasis. Hematoxylin and eosin stain, original magnification × 140.

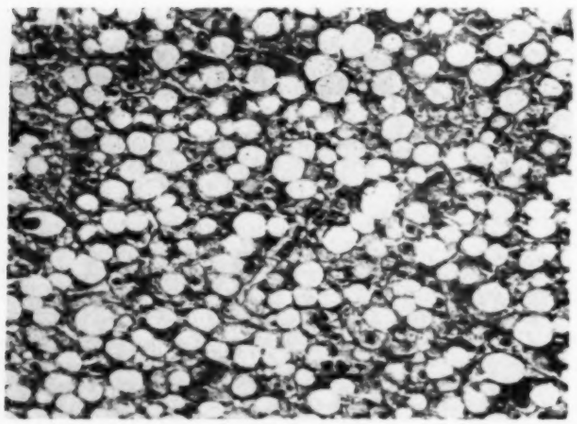


FIG. 2. Case IV. Photomicrograph of liver biopsy specimen obtained on fourteenth hospital day revealing marked fatty change and bile stasis. Hematoxylin and eosin stain, original magnification × 140.

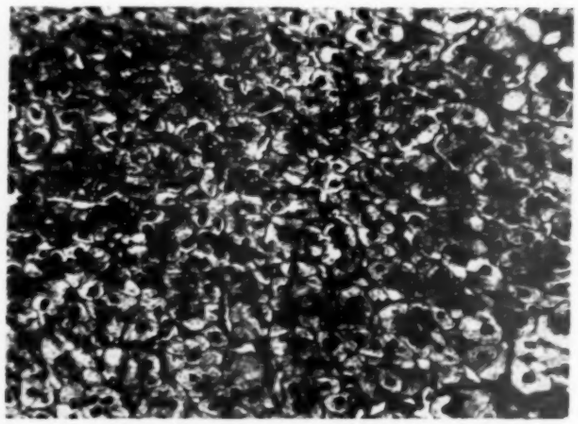


FIG. 3. Case IV. Photomicrograph of liver biopsy specimen obtained on fifty-first hospital day revealing slight fatty change. Hematoxylin and eosin stain, original magnification × 140.

7 cm. below the right costal margin. A fluid wave was thought to be present, and the abdomen was moderately distended. Edema of the ankles was present. No spider angiomas, palmar erythema or gynecomastia were noted. The temperature was 99°F., the pulse 92 and the respirations 22. The blood pressure was 120 mm. Hg systolic, 65 mm. Hg diastolic. Urinalysis revealed an alkaline reaction with a specific gravity of 1.014 and 1 plus reaction for albumin. Urobilinogen was present in a dilution of 1:10 and a result of a test for bile was positive. Examination of the blood revealed a hemoglobin of 10.2 gm. per cent, and a white blood cell count of 10,000 per cu. mm. Biochemical studies suggested obstructive jaundice. (Table I.) Percutaneous liver biopsy performed on the twenty-second hospital day revealed large amounts of fat, bile stasis and slight but definite increase in fibrous tissue in the portal areas. Therapy consisted of bed rest, adequate caloric intake and vitamin supplements. While on this regimen the liver edge regressed to just beneath the right costal margin and the biochemical abnormalities returned to normal. He remained asymptomatic throughout his hospital stay, gained a moderate amount of weight and was discharged on the forty-seventh hospital day.

CASE IV. V. C., a thirty-eight year old white man, a brewery truck driver, was admitted to the hospital on December 6, 1957, because of jaundice. Seven weeks prior to hospital entry the patient went on an alcoholic spree lasting four weeks, during which time he consumed 1 pint of whiskey and 16 to 20 pints of beer daily. One month prior to hospital entry he noted the onset of dark urine, light colored stools and scleral icterus. Two weeks preceding entry he noted intense pruritus. The caloric intake was grossly deficient throughout this period, which the patient attributed to anorexia, nausea and vomiting. The past history revealed a heavy alcoholic intake for twenty years.

Physical examination revealed a deeply icteric white man in no acute distress. The skin was covered with self-inflicted excoriations. Abdominal examination revealed a non-tender, firm liver edge 7 cm. below the right costal margin. There was pain upon pressure over both calves. Spider angiomas, splenomegaly, liver palms and gynecomastia were not present. The temperature was 99°F., the pulse 84, and the respirations 20. The blood pressure was 95 mm. Hg systolic, 70 mm. Hg diastolic. The urine was alkaline; the specific gravity was 1.012; the albumin content was 3 plus. Urobilinogen was not present in the urine; bile was present. Examination of the blood revealed a hemoglobin of 11.9 gm. per cent, and a white blood cell count of 7,200 per cu. mm. Several stool specimens were positive for occult blood. Biochemical studies suggested obstructive jaundice. (Table I.) Roentgenograms of the upper gastrointestinal tract suggested extrinsic compression of the first portion of the duodenum. Because of the high serum levels of bilirubin, alkaline phosphatase and cholesterol, and the negative reaction to cephalin-cholesterol flocculation and thymol turbidity tests, surgical exploration was undertaken on the fourteenth hospital day. At operation the liver was found to be enlarged, soft, distended and discolored with bile. Exploration of the common duct revealed no evidence of obstruction. Biopsy of the liver (Fig. 2) disclosed marked increase in fat, bile stasis and mild increase in fibrous tissue in the portal areas. Cholangiography revealed a normal biliary tract. The postoperative course was uneventful. The liver edge receded to the level of the right costal margin and the biochemical abnormalities returned to normal. During this period the patient gained 30 pounds in weight. A second liver biopsy (Fig. 3) performed six weeks following laparotomy revealed biliary stasis and small amounts of fat. The patient

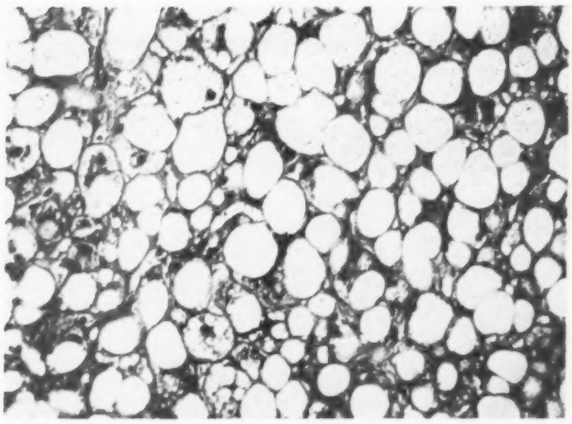


FIG. 4. Case V. Photomicrograph of liver biopsy specimen obtained on eighteenth hospital day revealing marked fatty change and bile stasis.

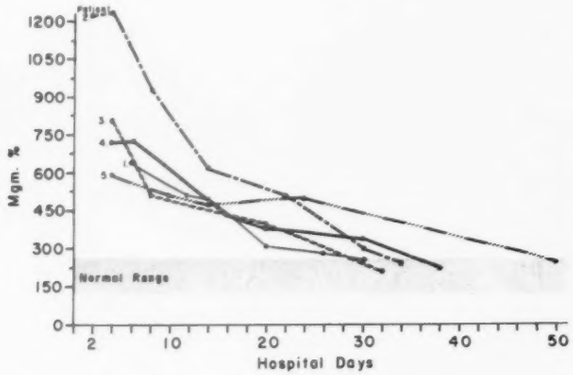


FIG. 5. Serial serum cholesterol levels during hospitalization. In all patients a progressive decline to normal levels occurred on conservative management.

was discharged on the 106th hospital day. At this time results of biochemical tests of liver function were normal and the patient was free of symptoms.

CASE V. J. A-O., a thirty-four year old Puerto Rican man, was admitted to this hospital on March 21, 1958, because of jaundice. During the three weeks immediately preceding hospital entry the patient experienced nausea, vomiting and considerable retching. Between episodes of vomiting he consumed about 1 pint of whiskey and several pints of beer daily. Abdominal pain was not present. Moderately severe anorexia with reduced caloric intake had been present for many weeks. Light colored stools and dark urine were first noted during the week of hospital entry. The patient gave no history of recent injections, transfusions or contact with jaundiced persons.

Physical examination revealed a well developed, well nourished, jaundiced man, with bilateral parotid swelling. The liver edge was firm and non-tender 8 cm. below the right costal margin. The edge of the spleen was felt 2 cm. below the left costal margin. Coarse tremors of both upper extremities were present. Biochemical studies suggested obstructive jaundice. (Table I.) Liver biopsy specimen (Fig. 4) revealed extensive fatty changes and a slight increase in fibrous tissue in the portal areas. Management consisted of bed rest and a high caloric diet with vitamin supplements. The hospital course was uneventful. Results of biochemical tests of liver function returned to normal concomitant with recession of the liver edge to the right costal margin. The spleen was not palpated at the time of discharge.

COMMENTS

The clinical features of these five patients are similar. All gave a history of chronic intake of alcohol in excess for months to several years, with significantly increased intake in the weeks just before admission. The history revealed very inadequate diet in three patients and one of borderline adequacy in the remaining two patients. Common symptoms were weakness, anorexia, nausea and vomiting. All patients described dark urine and light stools prior to admission. Each patient had an enlarged, firm liver palpable 6 cm. or more below the right costal margin. In all cases the total serum cholesterol exceeded 550 mg. per cent (Fig. 5), the serum alkaline phosphatase was between 32 and 92 King-Armstrong units. (Fig. 6.) Results of the cephalin cholesterol flocculation test were consistently negative in Cases I, II and III; a single determination of 1 plus was recorded in Case V, all others being negative, and values ranging from negative to 2 plus were obtained in Case IV. The reaction to the thymol turbidity test was consistently normal in all cases with the exception of a single elevated value of 6 units in Case I at the time of hospital entry. Biopsy of the liver in all cases revealed moderate to severe fatty metamorphosis and cholestasis. Slight fibrosis was present in two cases. In all patients an adequate diet and bed rest was associated with a diminution in liver size and a decrease of serum cholesterol, bilirubin and alkaline phosphatase to normal. (Figs. 5, 6 and 7.)

In addition to these features common to all patients, several other points deserve mention. The spleen was enlarged to palpation in the only patient with significant hepatic fibrosis (Case V) and was of normal size on discharge. In one case (Case IV) the clinical and laboratory findings were sufficiently suggestive of extrahepatic obstruction that exploratory laparotomy was performed.

The association of fatty liver and transient

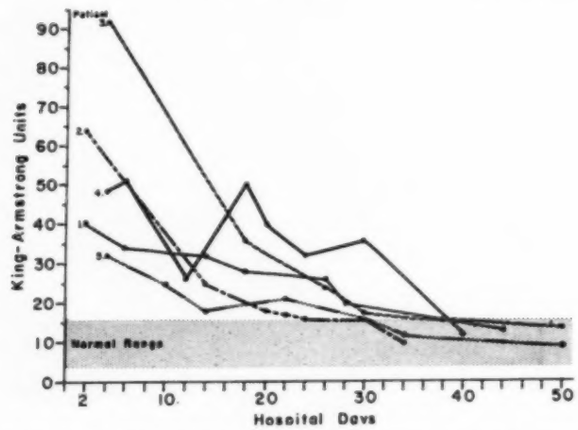


FIG. 6. Serial serum alkaline phosphatase values during course of hospitalization showing prompt decline to normal levels on conservative management.

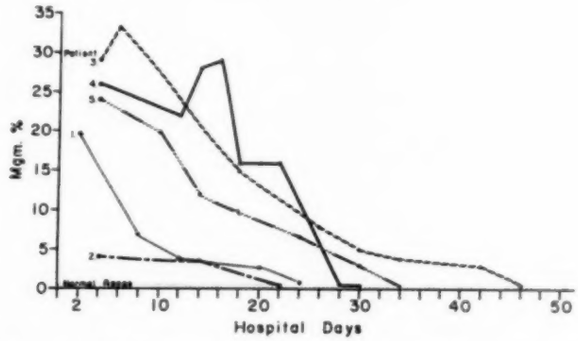


FIG. 7. Serial serum bilirubin values during course of hospitalization showing prompt decline to normal levels on conservative management.

jaundice observed in these cases has been noted on many occasions, but well documented cases are infrequently reported. Cases probably similar to those reported here are contained in larger series [*3–5,7,9*] but published details are often insufficient to permit satisfactory comparison. In 1953 Leevy reported a series of 102 patients in whom aspiration biopsy of the liver revealed fatty metamorphosis without fibrosis [*3*]. Twenty patients in this series were jaundiced, and in three the biochemical tests suggested obstructive jaundice. In these patients icterus gradually decreased as fat disappeared. Cholecystography showed normal visualization of the gallbladder when performed after maximum response to treatment. These three cases would appear to be quite similar to those reported herein.

The association of fatty liver with jaundice as a distinct clinical entity was reported by Popper [*4*] in 1953 when he described a series of cases characterized at autopsy by large, fatty livers and fatty cysts, but without cirrhosis or portohepatic anastomoses. Popper commented that, "Severe jaundice was associated with impairment of the tests indicating liver cell damage except that the thymol turbidity was often low and the alkaline phosphatase significantly elevated." Necrosis of the liver cells was invariably noted in the biopsy specimens and Popper considered the lesion a toxic hepatitis superimposed upon a fatty liver which had reduced resistance to infections or intoxications. The necrosis of liver cells and the degree of impairment of the tests which primarily reflect parenchymal cell damage would seem to distinguish these cases from the ones reported herein, but this difference may be simply quantitative.

In a clinical and pathologic study of fifty-six chronic alcoholics on the wards of the Boston City Hospital, Davidson [*5*] commented briefly on three jaundiced patients in whom the diagnosis of extrahepatic biliary obstruction was seriously considered. One of these three had undergone exploratory laparotomy. Biopsy specimens revealed moderate to marked amounts of fat, hyaline degeneration of the type described by Mallory [*6*], liver cell necrosis, parenchymal disorganization and fibrosis.

More recently Popper reported a series of ninety autopsy cases characterized by jaundice, probable hepatic failure, morphologic evidence of fatty metamorphosis and varying degrees of fibrosis. In thirty of these cases fatty changes were present without cirrhosis. In six of these thirty cases of fatty liver, the serum bilirubin was above 15 mg. per cent. Results of cephalin flocculation and thymol turbidity tests were frequently not abnormal whereas the alkaline phosphatase activity was frequently above normal limits.

Zieve [*9*] has described a group of twenty patients who exhibit some of the features noted in our five cases, but who differ in certain important aspects. They all had jaundice, hyperlipemia or hypercholesterolemia, and hemolytic anemia. The elevated serum cholesterol values in association with some elevation of alkaline phosphatase, slight or absent abnormality of the cephalin flocculation reaction and the presence of right upper quadrant or epigastric pain and tenderness led to the diagnosis of obstructive jaundice seven times [*9*]. A detailed description of the clinical and biochemical findings was presented in only one of these seven patients. He underwent exploratory laparotomy during the

fifth week of his illness because of hypercholesterolemia, elevated alkaline phosphatase and hyperbilirubinemia. Liver biopsy revealed minimal cirrhosis without mention of fatty content, and the thymol turbidity was 12 units. The similarity between this case and the ones reported herein is obvious. However, Zieve noted anemia in all his cases and concluded that the anemia was hemolytic in origin. In our cases, significant anemia was absent and Coombs' tests were therefore not performed. Although some degree of hemolysis is possible, the intrahepatic cholestasis noted in all biopsy specimens would seem to be a more important lesion to explain the hyperbilirubinemia. Hyperlipemia was not observed in our cases.

The not infrequent occurrence of hepatic steatosis and jaundice together suggests that the association is not fortuitous. The jaundice is not due to extrahepatic biliary obstruction nor is there biochemical or morphologic evidence of appreciable liver cell injury The most probable explanation for the jaundice would appear to be intrahepatic cholestasis. Mechanisms that have been proposed to explain the cholestasis are compresson of intrahepatic biliary radicles by fat cells or fatty cysts and/or increased permeability of the ductules [7]. Although the mechanisms by which jaundice results is unknown, hepatic steatosis exhibiting biochemical changes usually associated with obstructive disease of the biliary tree deserves special clinical emphasis. Indeed, it must be added to a rapidly increasing list of causes of obstructive jaundice for which surgical intervention is considered. If fatty metamorphosis is suspected, the diagnosis can be readily verified by a percutaneous liver biopsy.

SUMMARY

Five cases of fatty liver are presented. They are characterized by chronic use of alcohol in excess, jaundice, hepatomegaly and results of biochemical tests of liver function suggestive of biliary obstruction. Biopsy specimens of the liver revealed cholestasis and fatty metamorphosis with little or no cirrhosis. Rest and adequate diet resulted in prompt and complete remission of physical signs and restoration of abnormal biochemical tests of liver function to normal.

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Pulsations of the Liver in Heart Disease*

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THE clinical significance of a pulsating liver was emphasized by Mackenzie [*1*] in 1902 in relation to tricuspid stenosis. He thought that a presystolic pulsation of the liver was diagnostic of tricuspid stenosis. Subsequently, Turnbull and Weil [*2*] in 1911 recorded atrial liver pulsations in an eighteen year old patient with left-sided rheumatic lesion involving the mitral and aortic valves alone. In 1950 Grishman et al. [*3*] documented presystolic pulsations of the liver in patients with heart disease but with no tricuspid valvular lesion.

The present report illustrates hepatic pulse tracings in eight patients with heart disease. These patients have (1) tricuspid stenosis, (2) tricuspid incompetence with stenosis, (3) Ebstein's anomaly, (4) cor pulmonale due to multiple pulmonary infarction, (5) pericardial effusion, (6) constrictive pericarditis, (7) atrial septal defect and (8) myocarditis. The first three patients have tricuspid valve lesions and the last five are free from organic tricuspid valvular involvement.

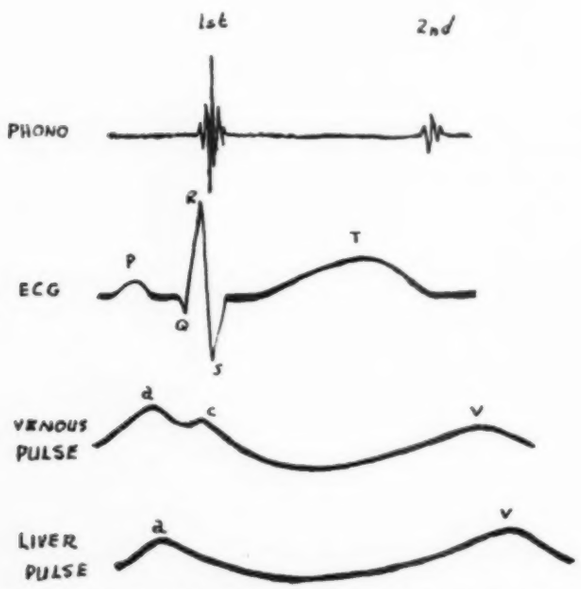


FIG. 1. Schematic drawing of the hepatic pulse in relation to the phonocardiogram, electrocardiogram, and the venous pulse.

METHOD OF RECORDING LIVER PULSATIONS

Hepatic tracings were taken using a pulse wave attachment connected to the AC input jack of the general purpose amplifier of a Sanborn Twin Beam Cardiette. A funnel type cup was fitted to the other end of the pulse wave attachment. The cup was held over the liver area with a steady pressure. Care was taken to place the cup lateral to the right mid-clavicular line to avoid epigastric pulsations transmitted from the right ventricle or abdominal aorta. A phonocardiogram was taken simultaneously for the purpose of timing the hepatic pulsations. In older patients, respiratory movements were minimized by taking the tracing during a temporary pause in inspiration or expiration.

NORMAL HEPATIC PULSE

The normal liver pulse consists of an "a" and a "v" wave. (Fig. 1.) The "a" wave is due to atrial contraction. During ventricular systole the normal hepatic pulse has a negative wave called "systolic collapse." This is apparently due to a decrease in liver volume as the hepatic veins empty into the inferior vena cava during ventricular contraction. The "v" wave occurs in early diastole and represents increase in hepatic volume. The "a" and "v" waves occur 0.02 and 0.004 second later than the corresponding waves in the jugular pulse.

The "c" wave normally found in jugular and in atrial pulse tracings is absent. According to Mackenzie the "c" wave of the jugular pulse is due to carotid pulsation. Grishman et al. [*3*] believe the impact of aortic pulsation on the superior vena cava during cardiac systole accounts for the "c" wave in the jugular pulse. The "c" wave in the atrial pulse tracing is attributed to the ballooning of the A-V valves into the atrium during ventricular systole.

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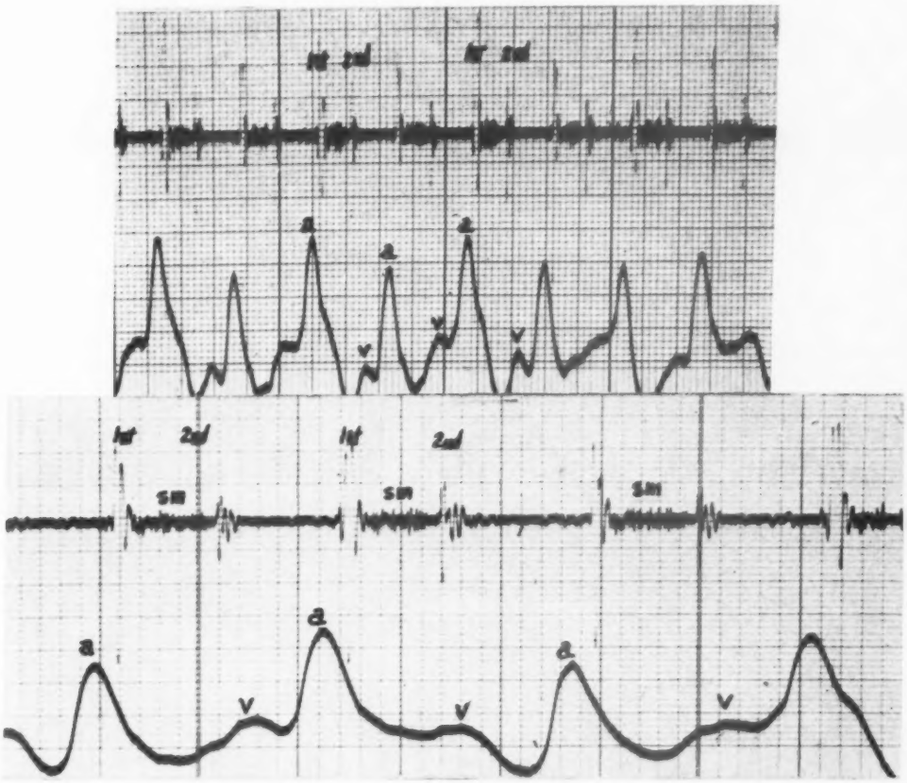


FIG. 2. Tall atrial (a) wave. Note the peak and the downstroke of (a) occur before the main vibration of the first (1st) sound. There is normal systolic collapse. (sm) systolic murmur.

CASE REPORTS

CASE I. A three month old boy had intermittent cyanosis and a pulsating liver. There was no evidence of congestive heart failure. The electrocardiogram showed left axis deviation and left ventricular preponderance for age. The chest roentgenogram showed a "square-shaped" heart with a normal transverse diameter. The diagnosis of tricuspid stenosis was confirmed by cineangiocardiography. A hepatic pulse tracing showed a huge "a" wave occurring before the onset of the first sound. (Fig. 2.)

CASE II. A fifty-six year old man with known rheumatic aortic stenosis was in severe congestive heart failure with 4 plus pitting pedal and pretibial edema and questionable ascites. The liver remained palpable and was noticed to pulsate despite improvement from congestive heart failure. The hepatic pulse tracing showed a systolic wave "en plateau" with a delayed and gradual rise and fall, occurring during ventricular systole. (Fig. 3.)

CASE III. An eighteen month old boy had cyanosis since the age of twelve months. The liver was enlarged and pulsated. A quadruple rhythm was present. The electrocardiogram showed incomplete right bundle branch block with slurring of lead R′ in lead V_1 and a borderline prolongation of the P-R interval for age and rate. In the chest roentgenogram the heart was enlarged and the pulmonary vascularity was diminished. A hepatic pulse tracing showed a tall "a" wave occurring before the onset of the first sound. (Fig. 4.)

CASE IV. An eight year old boy had had recurrent pulmonary emboli in the past year. The second pulmonic sound was loud, split and palpable. The liver was palpable and pulsated. There was no evidence of congestive heart failure. The electrocardiogram showed right ventricular hypertrophy. The chest roentgenogram revealed a prominent pulmonary conus, enlarged right ventricle, and soft infiltrate in both right and left upper lung fields. A prominent "a" wave was seen in the hepatic pulse tracing. (Fig. 5.) Autopsy findings confirmed the clinical diagnosis of pulmonary infarction and right ventricular hypertrophy.

CASE V. A five year old boy was admitted with fever and dyspnea. The liver was palpable with questionable pulsation. Congestive heart failure was absent. The electrocardiogram was diagnostic of acute pericarditis. The chest roentgenogram showed an enlarged cardiac silhouette with probable pericardial effusion. Pericardial tap produced 50 cc. of serosanguinous fluid. Culture of the pericardial fluid grew Salmonella choleraesuis. The hepatic tracing

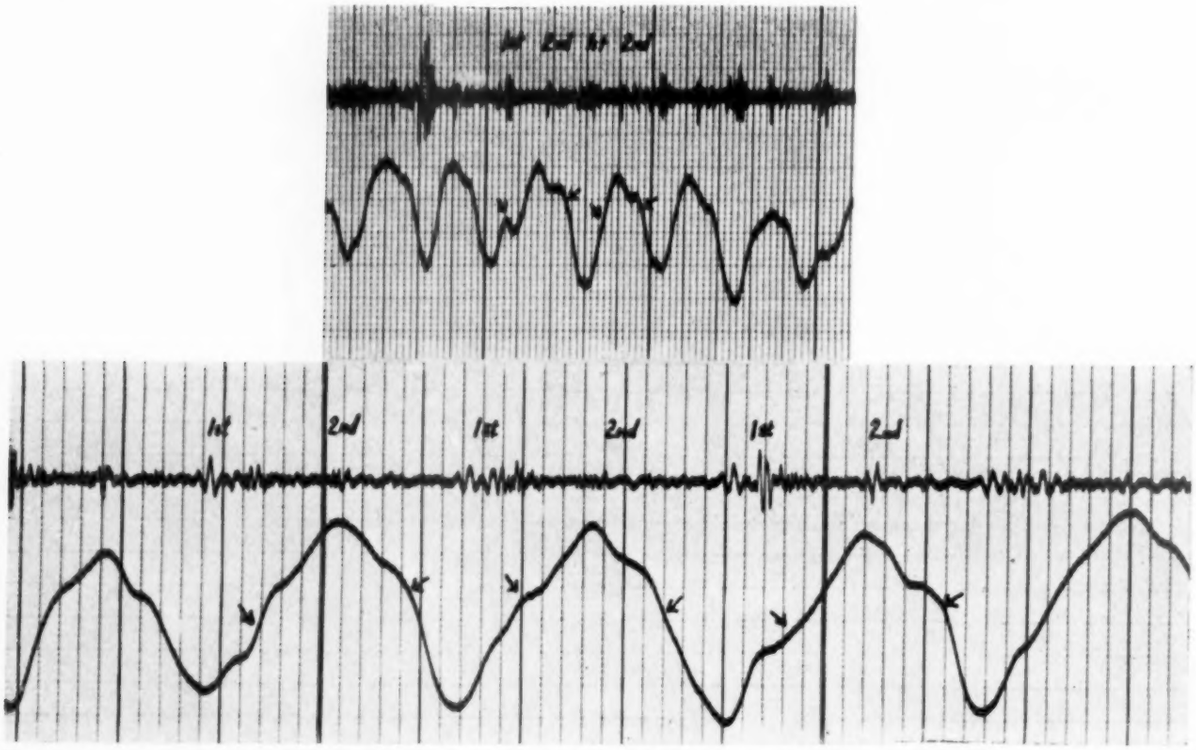


FIG. 3. Arrows indicate the systolic wave "en plateau." Note the delayed onset and the gradual rise and fall during the whole of systole. There is no atrial wave. Atrial fibrillation is present. Compare with Figure 2.

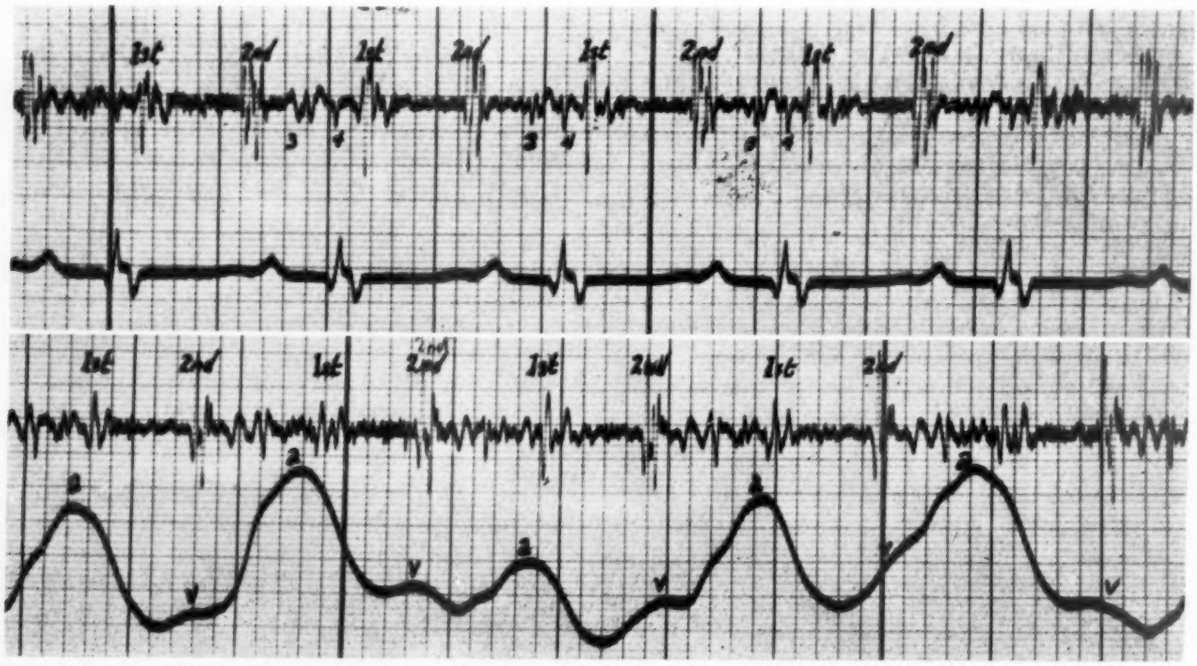


FIG. 4. Large atrial (a) wave. The peak occurs before the first (1st) sound. The phonocardiogram shows double atrial sound (3) and (4).

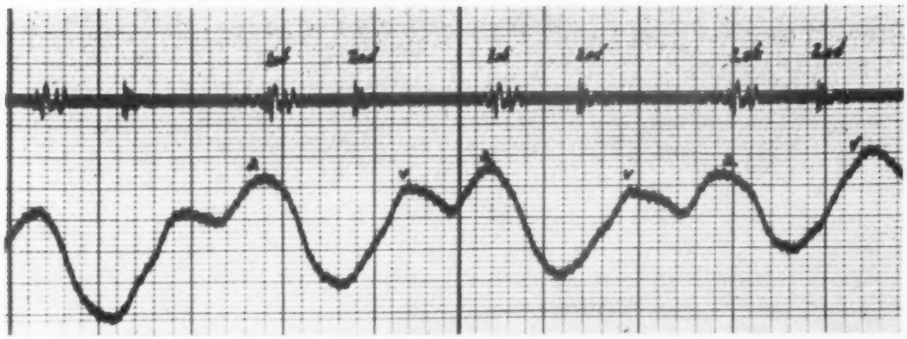


FIG. 5. Prominent atrial (a) wave. Compare with Figures 2 and 4.

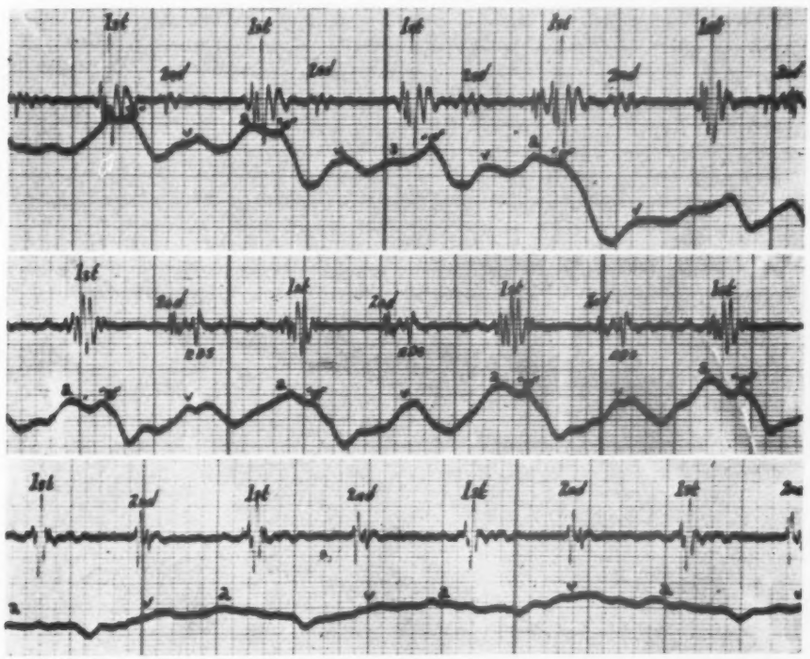


FIG. 6. *Top*, atrial (a) wave is not as tall as in Figures 2, 4 and 5 but still quite prominent. "P" represents an early systolic wave "en plateau." Functional tricuspid incompetence is present. Undulation of the baseline is due to respiration.

FIG. 7. *Middle*, note similarity of this tracing with Figure 6 above. The phonocardiogram shows an early diastolic sound (EDS). This tracing was taken before pericardectomy. *Bottom*, Tracing taken one month after pericardectomy. Normal (a) wave and no systolic wave "en plateau." The early diastolic sound is absent.

showed tall "a" wave with early systolic wave "en plateau." (Fig. 6.)

CASE VI. A fourteen year old girl complained of exertional dyspnea. The liver was not palpable. There was no evidence of congestive heart failure. The chest roentgenogram showed pericardial calcification. The hepatic pulse tracing demonstrated increased "a" wave and an early systolic wave "en plateau." The patient had an uneventful pericardiectomy. One month later another liver pulse tracing was taken which showed normal "a" and "v" waves. (Fig. 7.)

CASE VII. A four year old girl had a heart murmur since birth. A prominent "a" wave was seen in the jugular veins. The second pulmonic sound was widely split and accentuated. The liver was not palpable. There was no congestive heart failure. The electrocardiogram showed incomplete right bundle branch block. The chest roentgenogram revealed increased pulmonary vascularity and some degree of cardiac enlargement. The hepatic pulse tracing showed a tall "a" wave. (Fig. 8.) A large atrial septal defect measuring about 2 by 3 cm. was found at surgery.

CASE VIII. A three year old boy was admitted in

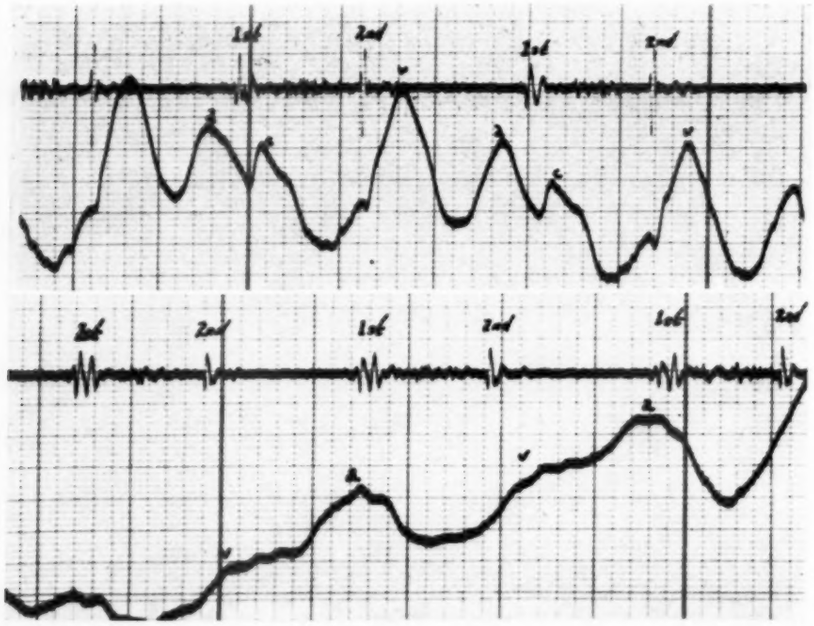


FIG. 8. *Upper*, jugular pulse tracing. Note a, c, and v waves. *Lower*, hepatic pulse tracing: Atrial (a) wave is prominent. Undulation of the baseline is due to respiration.

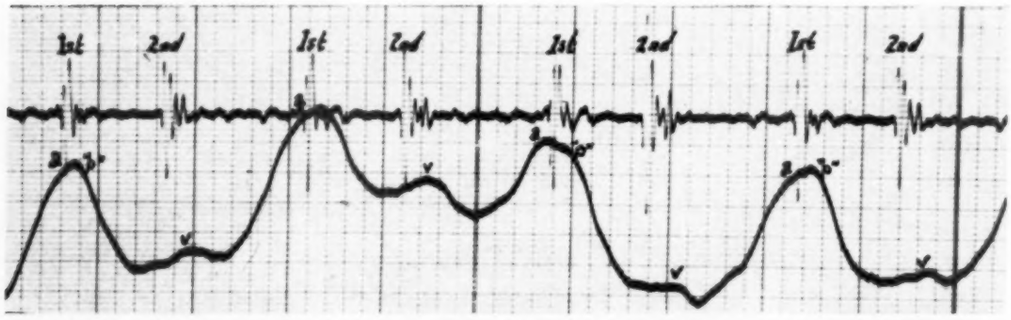


FIG. 9. Tall atrial (a) wave. The peak and downstroke of (a) occur with the first (1st) sound and early systole. "P" represents an early systolic wave "en plateau" fused with the (a) wave. Functional tricuspid incompetence is present. Compare with Figures 2, 4, 5, 6 and 7.

severe congestive heart failure. The liver was palpable with questionable pulsations. The electrocardiogram showed S-T and T changes consistent with myocarditis. The chest roentgenogram showed hilar congestion and an enlarged heart. The etiology of the myocarditis remains unknown. A huge "a" wave fused with an early systolic wave was present in the hepatic pulse tracing. (Fig. 9.)

COMMENTS

Abnormal pulsations of the liver are either presystolic (atrial) or systolic in time in relation to the cardiac cycle. The accentuation of the normal "a" wave gives rise to a large presystolic or atrial liver pulse. With a normal sinus rhythm the term "presystolic" is correct. When the atria and the ventricles contract simultaneously or almost simultaneously, as in certain types of arrhythmias, the "a" wave of the hepatic pulse may occur during ventricular systole. In the presence of atrial fibrillation, a situation in which an effective and strong atrial contraction is wanting, the "a" wave is absent. For these reasons, "atrial" is preferable to "presystolic" in describing the "a" wave of the hepatic pulse.

A positive systolic wave in the liver pulse is always abnormal. It represents tricuspid incompetence if an "a" wave produced by an arrhythemia is excluded. This positive wave is called systolic wave "en plateau." It is due to retrograde transmission of a pulse wave resulting from right ventricular contraction. The extra load on the right atrium and the great veins provided by

the regurgitant blood may be an additional factor in the genesis of this wave.

Atrial Pulsations. Conditions producing prominent atrial pulsation of the liver may be due to systolic or to diastolic overloading of the right atrium or both. (Table I.)

The entrance of both superior and inferior venae cavae into the right atrium is not protected by any competent valve structure. Reflux of dye into the great veins during the rapid injection of dye into the right atrium is commonly seen in angiocardiograms or cineangiocardiograms. The retrograde transmission of the pressure wave from a strong right atrial contraction (or from the contraction of the left atrium transmitted through an atrial septal defect) down the inferior vena cava to the liver produces the prominent "a" wave in these conditions.

Clinically, anatomic obstruction to right atrial outflow is seen in congenital tricuspid atresia in its complete form. An atrial septal defect must exist to sustain life. Partial obstruction is found in tricuspid stenosis, commonly acquired and rarely congenital (Case I). Usually acquired tricuspid stenosis is part of a multivalvular rheumatic involvement. Differentiation between congenital tricuspid stenosis and atresia is now possible during life by cineangiocardiography [*4*]. Since both these conditions show prominent "a" waves, the hepatic tracing adds no further help in the differential diagnosis. However, a hepatic pulse tracing may be helpful in ruling out congenital tricuspid incompetence.

Certain disturbances in cardiac rhythm give rise to a prominent "a" wave in the jugular pulse as well as in the hepatic pulse tracing. Examples of such arrhythemias are complete A-V block or A-V dissociation, atrial flutter or atrial tachycardia with A-V block, double tachycardias and some types of nodal rhythm. Large "a" waves are produced when atrial contraction occurs simultaneously with ventricular systole. In this instance the A-V valves are closed temporarily because of ventricular contraction. The force of atrial contraction therefore can be propagated only retrograde to the jugulars and to the liver.

In pure pulmonic stenosis (ventricular septum intact) prominent "a" waves are commonly seen in the jugular pulse. In fact if pulmonary stenosis is suspected and no prominent "a" wave is visible in the jugular vein an associated ventricular septal defect must be considered.

TABLE I
CONDITIONS PRODUCING INCREASED ATRIAL LIVER PULSATIONS

I. Systolic overloading of the right atrium
  A. Obstruction to right atrial outflow
    1. Anatomic
      Tricuspid atresia—congenital
      Tricuspid stenosis—acquired or congenital
    2. Physiologic
      Disturbances of rhythm—complete A-V block, etc.
  B. Obstruction to right ventricular outflow
    1. Pulmonary artery atresia—congenital
      Pulmonic stenosis—valvular, infundibular or both
    2. Pulmonary hypertension—primary or secondary
  C. Restriction of right ventricular filling
    1. Pericardial effusion, constrictive pericarditis
    2. Ebstein's anomaly
II. Diastolic overloading of the right atrium
  A. Left to right shunt at the atrial level—atrial septal defect, patent foramen ovale, Lutembacher syndrome, rupture of sinus of Valsalva into the right atrium, anomalous pulmonary veins
III. Combination of I and II
  A. Congestive heart failure complicating conditions in I and II
  B. Primary myocardial disease with congestive heart failure
    1. Myocarditis—specific or non-specific

Right ventricular pressure is increased in pulmonary stenosis and pulmonary hypertension (Case IV). This increase in right ventricular pressure raises the resistance to outflow of the right atrium. Figure 10 shows a jugular pulse tracing in a patient with pure pulmonic stenosis. Catheterization data did not reveal any evidence of a shunt.

The diastolic filling of the right ventricle is restricted in pericardial effusion (Case V) and in constrictive pericarditis (Case VI). It is possible that extracardiac masses pressing on the ventricular chambers may produce the same effect. The third sound called "protodiastolic knock" heard in some cases of constrictive pericarditis has been related to the early diastolic check to ventricular filling by the calcified pericardial shell. The third heart sound coincides with the early diastolic dip in a ventricular pressure tracing. Figure 6 shows the third sound in the phonocardiogram above the hepatic pulse curve before operation. After pericardiectomy the third sound disappeared and the hepatic pulse tracing returned to normal.

Ebstein's anomaly (Case 3) presents an interesting congenital malformation of the tricuspid valve. The anterior and posterior leaflets are

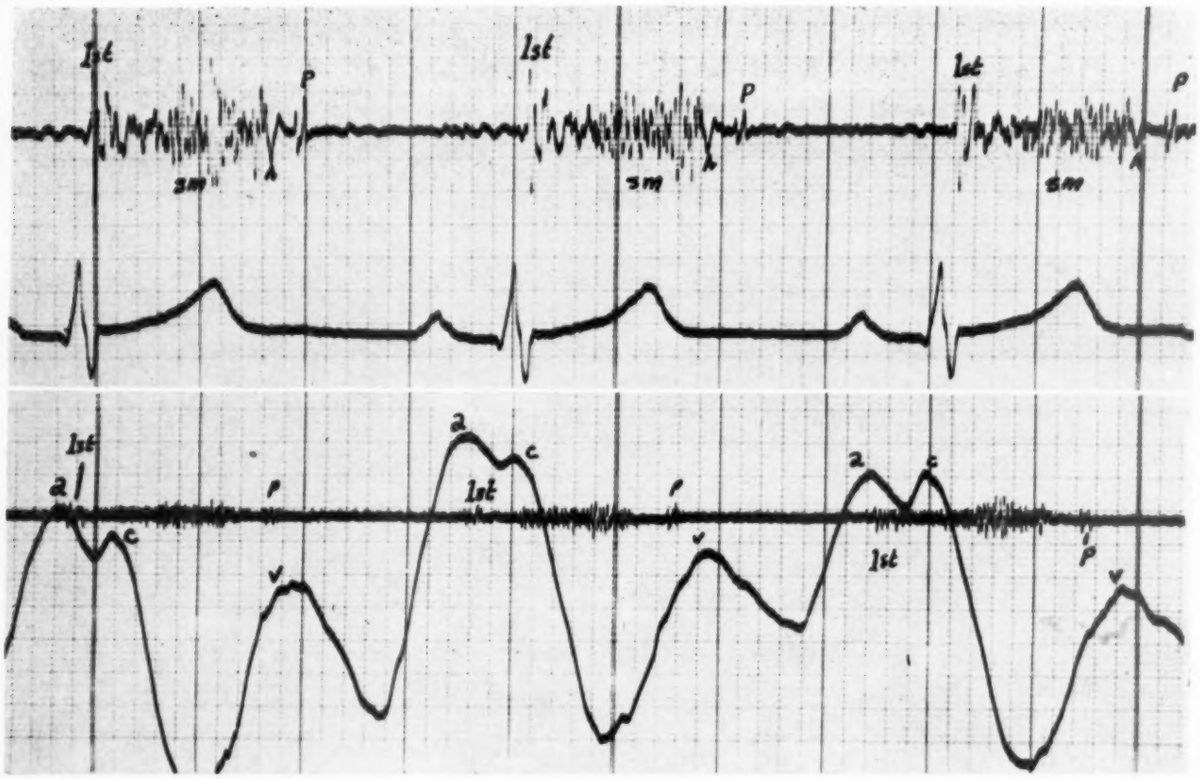


FIG. 10. Jugular pulse tracing: Tall atrial (a) wave. The phonocardiogram shows a systolic murmur (sm) termination clearly before the pulmonic (P) component of the second sound. (A) aortic component of the second sound.

fused and displaced downward into the cavity of the right ventricle. The right atrium becomes greatly enlarged at the expense of the right ventricular chamber. Frequently there is an associated atrial septal defect or a patent foramen ovale. The reduction in size of the cavity of the right ventricle limits ventricular filling in this condition. The shunt at the atrial level may be bidirectional, hence the absence of cyanosis does not rule out the diagnosis of Ebstein's anomaly.

Diastolic overloading of the right atrium as a result of a left to right shunt at the atrial level (Case VII) increases the work load of the right atrium. This produces a strong atrial contraction. Myocardial weakness due to myocarditis (Case VIII) imposes a condition of relative diastolic overloading of the ventricles. The right ventricle, being the weaker ventricle, may fail earlier than the left. The decreased output of the former may spare the latter. When right ventricular failure develops, the end diastolic pressure in the right ventricle becomes elevated and the right atrial pressure also rises. In combined left and right ventricular failure the situation is more complex. A combination of factors, including increase in circulating blood volume, may be at work. Half of the patients reported by Grishman et al. [*3*] were in congestive heart failure of moderate to severe degree. In this report severe congestive heart failure was present in Cases II and VIII.

Systolic Pulsations. Systolic pulsation of the liver is classically found in tricuspid incompetence, functional or organic. Lottenbach and Shillingford [*5*] have verified tricuspid incompetence at autopsy in ten patients with congestive heart failure whose mean venous pressure during life was greater than 8 mm. Hg. They postulated that tricuspid incompetence was produced first, by the dilated right ventricle pulling down the chordae attached to the edge of the valve, and second by the general dilatation of the valve ring. According to Hollman [*6*] the tricuspid valve is anatomically prone to incompetence in comparison with the mitral valve. It is probably true that functional tricuspid incompetence does occur in most cases of frank congestive heart failure.

Organic tricuspid incompetence is usually due to rheumatic valvulitis. Incompetence almost always accompanies rheumatic tricuspid

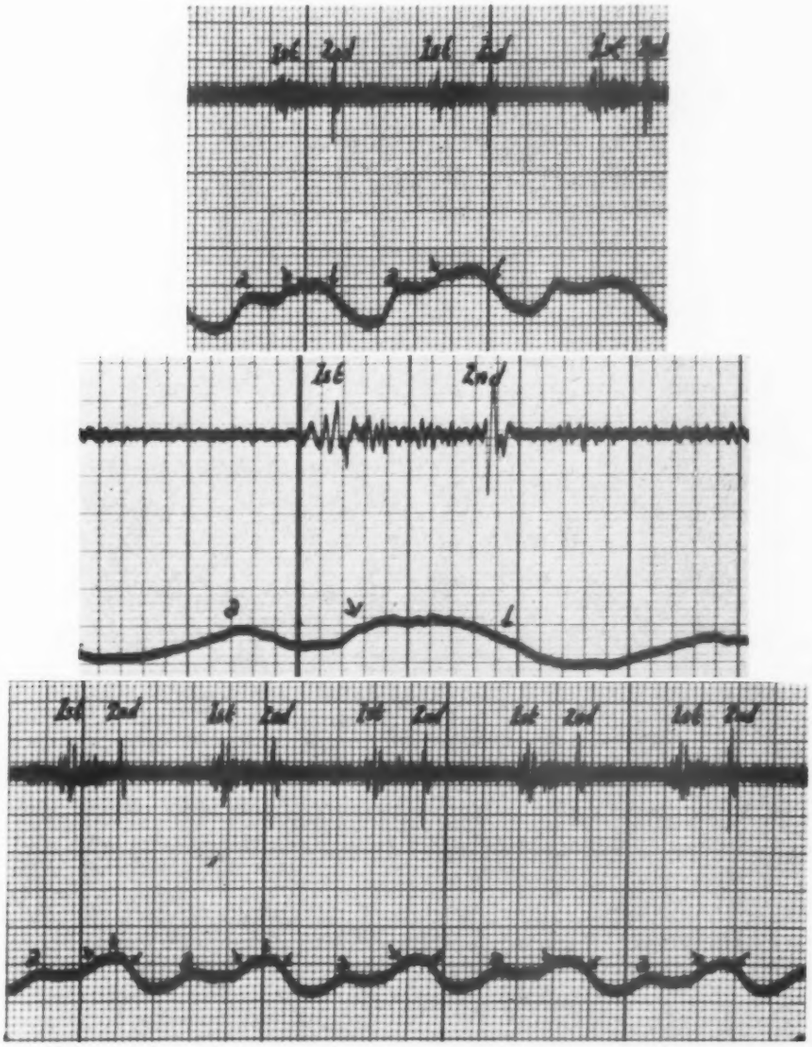


FIG. 11. *Top* and *middle* are jugular pulse tracings taken at 25 mm. and 75 mm. per second, respectively. *Bottom*, hepatic pulse tracing taken at 25 mm. per second. Arrows indicate systolic wave "en plateau." Atrial wave (a) is present. Compare with Figure 3. (See text.)

stenosis (Case II). Congenital tricuspid incompetence is rare [7].

Both organic and functional tricuspid incompetence are characterized by a systolic wave "en plateau" in the hepatic pulse tracing. The differentiation between the two may prove difficult at times. Usually in functional tricuspid incompetence the plateau wave comes early in systole; it may fuse with the downstroke of the "a" wave. In organic tricuspid incompetence the "en plateau" wave has a delayed onset with a gradual rise and fall. The reason for this is the fact that acquired organic tricuspid incompetence usually accompanies stenosis of the valve as well. Figure 3 shows the hepatic pulse tracing obtained in Case II. Typically, the plateau wave is delayed in onset; the rise is gradual and the fall is slow.

Recently, Terry [8] described a new physical sign in tricuspid incompetence called "coupled hepatic pulsation." He found that ventricular extrasystoles may be helpful in distinguishing intrinsic hepatic pulsations due to tricuspid incompetence from hepatic pulsations transmitted from the abdominal aorta. By holding one hand over the liver and the other over a peripheral artery one will notice that in the presence of a ventricular extrasystole no pulse will be felt in the peripheral artery. However, a pulsation will be felt over the liver if tricuspid

incompetence exists. This sign becomes more obvious in coupled rhythm due to ventricular extrasystoles.

Correct timing of hepatic pulsations may be difficult by palpation and/or inspection alone. In the presence of a tachycardia the difficulty is magnified. In addition, the weaker atrial (presystolic) pulsation may not be appreciated by the palpating hand as a pulse wave separate from the usually stronger systolic pulsation, even with a normal sinus rhythm. In atrial fibrillation the "a" wave is absent and the systolic wave "en plateau" becomes more pronounced because tricuspid incompetence is increased. In Figure 3 the "a" wave is absent because the tracing was taken when the patient was in atrial fibrillation. Figure 11 is a tracing obtained from another patient with tricuspid stenosis with incompetence. Sinus rhythm and the "a" wave are present. Again the systolic wave "en plateau" is delayed in onset.

By taking a hepatic pulse tracing, timing of liver pulsations is rendered easy and accurate. Recent advances in tricuspid valve surgery [*9,10*] have made correct timing of hepatic pulsations of more than academic interest. Consideration of a patient for possible surgery of the tricuspid valve demands precise diagnosis of the valvular lesion—stenosis, incompetence, or both. In this regard, a hepatic pulse tracing may be helpful in corroborating the findings in the catheterization of the right heart and in cineangiocardiography [*4*].

A palpable liver is one of the cardinal signs of congestive heart failure. Mechanical obstruction to venous return of the right heart, as found in tricuspid valvular disease and in pericarditis, may produce hepatic enlargement with or without palpable or visible pulsation, edema or ascites in the absence of actual failure of the myocardium. Experimental studies [*11,12*] have demonstrated increased secretion of aldosterone in dogs with thoracic inferior vena cava constriction. An increase in aldosterone secretion may well be a factor in the production of liver engorgement, edema and ascites in tricuspid and pericardial disease. It is clinically important that the mere presence of these signs should not be construed hurriedly as evidence of congestive heart failure and, therefore, an indication for digitalization. Conversely, in a patient (usually a female) with known rheumatic heart disease involving the mitral and/or aortic valve, persistence of signs of right-sided heart failure should call attention to tricuspid valvular involvement.

SUMMARY

The clinical importance of pulsations of the liver in different heart conditions is summarized and the pathogenesis of these pulsations is explained. Eight case reports illustrating abnormal liver pulsations are presented. The value of correct timing of liver pulsations by taking hepatic pulse tracings is emphasized in the light of recent advances in tricuspid valve surgery

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Alterations in Indices of Liver Function in Congestive Heart Failure with Particular Reference to Serum Enzymes*

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IN 1930 Jolliffe [*1*] first demonstrated that liver function tests were deranged in patients with congestive heart failure, and that these altered functions returned to normal following restoration of adequate compensation. White et al. [*2,3*] and Sherlock [*4*] attempted to correlate alterations in liver function tests with histologic evidence of necrosis or atrophy of hepatic cells by performing serial aspiration biopsies or post-mortem examination of the liver in patients with congestive heart failure. Evans [*5*] attempted to correlate hepatic dysfunction with reduction in hepatic blood flow and oxygen saturation, as measured by hepatic vein catheterization.

Since the appearance of these and other [*6–9*] reports new indices for evaluating liver function have been developed, particularly measurement of various serum enzymes. It is the purpose of this report to attempt to correlate a variety of liver function tests with the clinical course of cardiac decompensation in patients with right sided congestive heart failure.

PATIENTS STUDIED

Indices of liver function were determined in 175 patients with right-sided congestive heart failure due to various causes. (Table I.) No attempt was made to select patients according to the severity or etiology of the failure. Patients were classified as having acute or chronic right heart failure, depending upon the duration and severity of the decompensation: acute failure if symptomatic distress and associated clinical findings occurred within fourteen days prior to study and progressed rapidly, and chronic failure if of longer duration and without progression during the preceding two weeks. The acute category included not only patients with the initial onset of failure, but also those with acute exacerbation of previously well controlled failure. The patients with acute failure generally had a much more severe degree of decompensation, of shorter duration, than those with chronic failure. The incidence of most of the physical findings related to right heart failure was only slightly higher in the former: hepatomegaly occurred in 99 and 95 per cent of the two groups, hepatic enlargement of more than 5 cm. below the right costal margin in 57 and 49 per cent, peripheral edema in 77 and 71 per cent, and pleural effu-

TABLE I
CAUSES OF RIGHT-SIDED HEART FAILURE IN PATIENTS STUDIED

Causes of Failure	Patients Studied			
	No.	%	No. with Acute Failure	No. with Chronic Failure
Arteriosclerotic heart disease	58	33.1	34	24
Hypertensive heart disease	38	21.7	29	9
Rheumatic heart disease	56	32.0	33	23
Cor pulmonale	10	5.7	5	5
Constrictive pericarditis	7	4.0	1	6
Congenital heart disease	3	1.7	1	2
Scleroderma heart disease	1	0.6	1	0
Syphilitic heart disease	1	0.6	1	0
Ball valve thrombus	1	0.6	1	0

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TABLE II
RESULTS IN PATIENTS STUDIED

Indices of Liver Function	Acute Failure		Chronic Failure		Arterio-sclerotic		Hyper-tensive		Rheumatic		Cor Pulmonale		Constrictive Pericarditis	
	No.	Ab-normal (%)*	No.	Ab-normal (%)	No.	Ab-normal (%)	No.	Ab-normal (%)	No.	Ab-normal (%)	No.	Ab-normal (%)	No.	Ab-normal (%)
Excretory														
Bilirubin†	86	37	57	21	47	23	32	31	47	45	5	100	7	14
Bromsulfalein retention	71	87	55	71	41	76	27	82	43	79	5	100	6	83
Alkaline phosphatase	80	10	55	9	43	16	27	4	44	9	8	0	7	0
Cell destruction														
SGOT	67	48	37	5	32	31	24	42	35	29	8	38	2	0
SGPT	53	15	29	3	25	16	18	11	32	6	4	25	2	0
Abnormal proteins														
Globulin	100	60	67	37	57	46	35	46	53	60	9	56	7	29
Thymol turbidity	67	3	52	0	40	0	23	0	39	5	7	0	7	0
Biosynthetic functions														
Cephalin-flocculation test	71	21	48	17	33	9	26	15	41	39	7	0	7	14
Prothrombin	68	84	43	74	37	78	25	76	36	81	5	100	4	75
Albumin	100	32	67	27	57	28	35	26	53	32	9	44	7	29
Cholinesterase	32	54	32	44	23	54	21	40	16	17	2	67	2	100
Cholesterol	87	49	60	42	52	42	30	37	43	49	7	71	7	71
Cholesterol esters	51	41	39	31	34	32	18	22	26	46	5	40	4	50

* Serum bilirubin, BSP retention, SGOT, SGPT, globulin, cephalin-flocculation and thymol turbidity above normal range; prothrombin concentration, albumin, cholinesterase, cholesterol and cholesterol esters below normal range.
† Serum bilirubin may also be an index of cell destruction.

sion in 25 and 17 per cent. Splenomegaly was of equal incidence in the two groups (20 and 22 per cent), and ascites more common in the latter (7 and 20 per cent).

Patients with evidence of myocardial infarction were excluded from the study as this process results in elevation of serum transaminase activity, while those with evidence of pulmonary infarction were excluded since this may result in increased serum bilirubin concentration, and occasionally increased transaminase.

METHODS

The indices of liver function that were studied may be classified as those measuring primarily excretory function (serum bilirubin,* bromsulfalein [BSP] retention, and alkaline phosphatase activity); those reflecting mainly cell destruction (serum glutamic oxalacetic transaminase [SGOT] and glutamic pyruvic transaminase [SGPT]); those reflecting production of abnormal proteins (serum globulin and thymol turbidity); and those reflecting decreased biosynthesis (serum cephalin flocculation [CCF], plasma prothrombin concentration, serum albumin, cholinesterase activity, cholesterol, and cholesterol esters). The normal range of values for these indices of liver function, and the methods employed (indicated by reference numbers) were as follows: bilirubin [*10*] 0 to 1.2 mg. per cent; bromsulfalein retention [*11*] 0 to 8 per cent forty-five minutes after intravenous injection of the dye; alkaline phosphatase [*12*] 3 to 12 King-Armstrong units; SGOT and SGPT [*13*] 0 to 40 units; serum globulin [*14*] 2 to 3.5 gm. per cent; thymol turbidity test [*15*] 0 to 10 units; cephalin flocculation test [*16*] 0 to 2 plus; prothrombin concentration [*17*] more than 85 per cent of normal; serum albumin [*14*] 3 to 4.5 gm. per cent; serum cholinesterase activity [*18*] 0.65 to 1.4 Δ pH per hour; serum cholesterol [*19*] 185 to 260 mg. per cent; and cholesterol esters [*20*] 130 to 220 mg. per cent. In addition to these indices of liver function, fasting blood sugar [*21*] (normal range 60 to 100 mg. per cent) and blood urea nitrogen [*22*] (normal range 18 to 25 mg. per cent), venous pressure and circulation time were determined.

Indices of hepatic function were determined initially and at intervals during exacerbation or compensation of cardiac failure. Liver tissue was examined in nineteen patients following biopsy or postmortem examination.

* Serum bilirubin concentration may also reflect cell destruction.

RESULTS

Table II and Figures 1 and 2

Indices of Excretory Function. Bilirubin: The serum concentration of bilirubin was elevated in 31 per cent of patients, but only 5 per cent had visible jaundice, with a serum bilirubin above 3 mg. per cent. Elevation of serum bilirubin was more frequent in patients with acute failure (37 per cent) than in those with chronic failure (21 per cent), and was also more marked in the

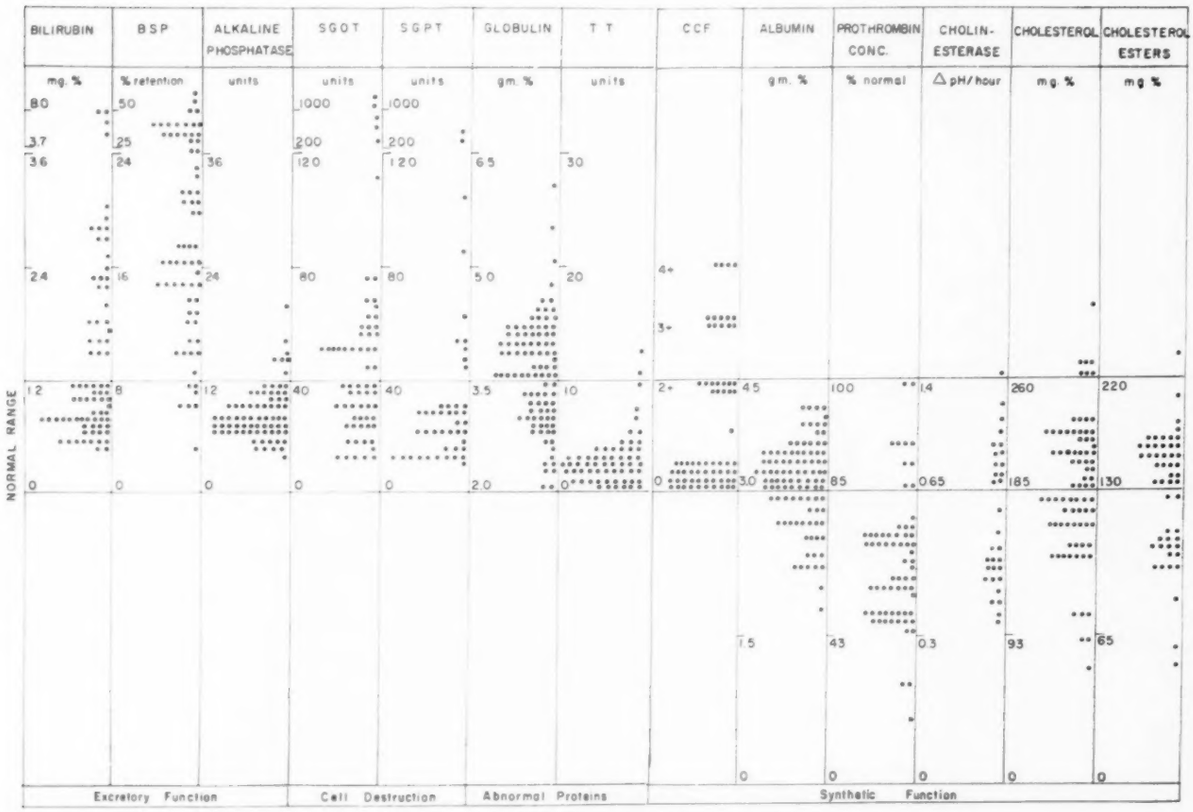


FIG. 1. Indices of liver function in patients with acute right heart failure.

former. The highest level was 8 mg. per cent. The higher values were usually accompanied by elevated serum transaminase values, particularly SGOT, and by histologic evidence of centrilobular hepatic cell necrosis. The highest incidence of bilirubinemia occurred in patients with acute right heart failure due to rheumatic heart disease, particularly with tricuspid stenosis or insufficiency, or due to cor pulmonale. In all patients the bilirubinemia fluctuated with the severity of right heart failure, and 87 per cent had marked improvement in this index following compensation, usually over a period of three to seven days.

Bromsulfalein Retention. This was the most sensitive index of hepatic dysfunction, showing abnormal results in 80 per cent of the patients. Abnormal retention of dye was somewhat more frequent in patients with acute failure (87 per cent) than in those with chronic failure (71 per cent), and was usually more marked in the former The most pronounced change was 66 per cent retention. All patients whose failure could be compensated showed marked improvement in bromsulfalein excretion, usually over a period of about a week.

Alkaline Phosphatase. The serum level of this enzyme was increased in only 10 per cent of patients and was the same in patients with acute and chronic failure. The elevation was usually slight, the highest values (16 to 21 units) being found in patients with enormously distended livers.

Indices of Cell Destruction. SGOT: This was elevated in 33 per cent of patients, increases being limited almost entirely to patients with acute failure, of whom 49 per cent had elevated SGOT activity, compared to 5 per cent of patients with chronic failure. Four-fifths of the elevations were between 40 and 80 units, but the remainder ranged as high as 1,250 units. The highest values (500 to 1,250 units) occurred in patients with severe acute right heart failure due to rheumatic heart disease with tricuspid insufficiency, or due to cor pulmonale. Marked elevation was accompanied by increase in serum bilirubin concentration. Improvement in right heart failure was accompanied by rapid reduction in

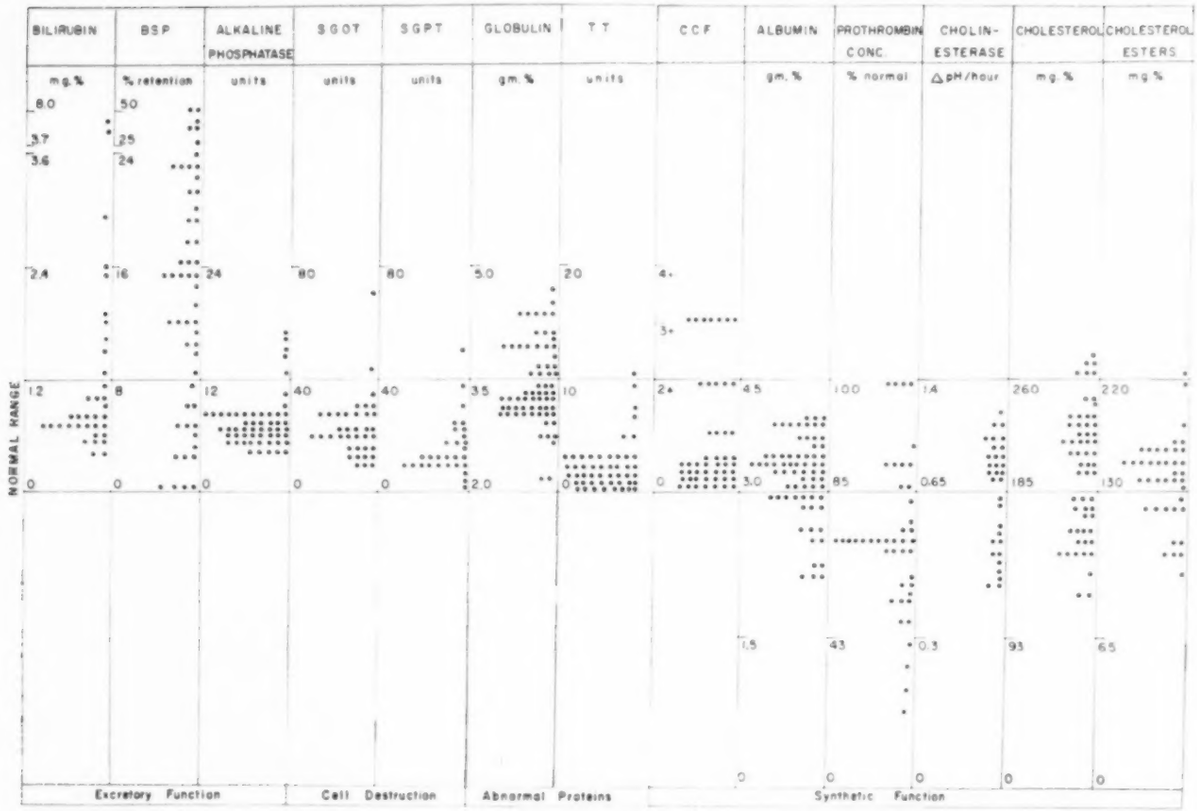


FIG. 2. Indices of liver function in patients with chronic right heart failure.

transaminase activity, the greatest change occurring during the first day or two, and return to normal activity usually within three to seven days.

SGPT. This was elevated in 11 per cent of patients. As with SGOT activity, the elevation was much more frequent in patients with acute failure (15 per cent) than with chronic failure (3 per cent), and was more marked in the former. Most of the increases were between 40 and 80 units. The highest value was 530 units. Elevation of SGPT tended to parallel that of SGOT, but was usually less marked. The relationship to type of right heart failure, serum bilirubin concentration, and compensation of the failure was similar to that of SGOT activity.

Indices of Abnormal Protein Production. Globulins: Hyperglobulinemia occurred in 51 per cent of patients, and was more common in those with acute failure (60 per cent) than with chronic failure (37 per cent). However, the degree of change was not marked: in three-fourths of the patients with increased globulins the serum concentration was between 3.5 and 4.1 gm. per cent. The highest incidence and degree of hyperglobulinemia occurred in patients with right heart failure due to rheumatic heart disease or cor pulmonale, the highest value being 6.1 gm. per cent. Compensation of failure was followed by little change in serum globulin concentration.

Thymol Turbidity. This gave abnormal results in only 2 per cent of patients, the change occurring in two patients with acute right heart failure due to rheumatic heart disease. Both elevations reached only 12 units.

Indices of Biosynthetic Functions. Cephalin-Flocculation: Results of this test were abnormal in 19 per cent of patients. The incidence of the abnormality was approximately the same in patients with acute and chronic failure (21 per cent and 17 per cent), but tended to be slightly more marked in the former. The highest incidence of abnormality was in patients with right heart failure due to rheumatic heart disease (39 per cent), in whom the test was frequently 4 plus. Compensation of failure was followed by slow and partial decline in the cephalin-flocculation reaction over a period of one or more months.

Albumin. Hypoalbuminemia occurred in 30 per cent of patients. The incidence was ap-

proximately the same in patients with acute and chronic failure (32 per cent and 27 per cent), as was the degree. The changes were not marked: in three-fourths of the patients with depressed serum albumin the concentration was between 2.5 and 2.9 gm. per cent. The lowest value was to 1.6 gm. per cent. The incidence of abnormality was highest in patients with right heart failure due to rheumatic heart disease or cor pulmonale. When the heart failure was compensated, the serum albumin rose slowly over a period of one or more months in half the patients.

Prothrombin Concentration. This was depressed in 80 per cent of patients. This incidence was equal to that of abnormal bromsulfalein retention, although the changes were usually not as marked. Hypoprothrombinemia was slightly more common in patients with acute failure (84 per cent) than with chronic failure (74 per cent). In most instances the prothrombin concentration was between 50 and 85 per cent of normal, but in a few patients with either acute or chronic failure the concentration was as low as 20 to 30 per cent. The parenteral administration of vitamin K had little or no effect on the prothrombin concentration. However, with compensation of the right heart failure 73 per cent of patients showed improvement in this index, usually over a period of two to three weeks.

Cholinesterase Activity. This was depressed in 48 per cent of patients, slightly more frequently in patients with acute failure (54 per cent) than with chronic failure (44 per cent), and slightly more marked in the former. The lowest value obtained was 0.33 Δ pH per hour, which is half the lower limit of normal activity. With improvement in heart failure there was usually some rise in serum cholinesterase activity over a period of about one month.

Cholesterol. Serum cholesterol was depressed in 46 per cent of patients. The depression was slightly more frequent in patients with acute failure (49 per cent) than with chronic failure (42 per cent), and the lowest values (78 mg. per cent) were encountered in the former, particularly in patients with elevated serum transaminase activity. With compensation of heart failure the serum cholesterol usually rose slowly over a period of about one month in patients with acute failure, but remained depressed in most patients with chronic failure.

Cholesterol Esters. These were depressed in 37 per cent of patients. The incidence was higher in patients with acute failure (41 per cent) than with chronic failure (31 per cent) and the lowest values were encountered in the former group, particularly in patients with elevated serum transaminase activity. Patients with rheumatic heart disease had the greatest incidence (46 per cent) and degree of change among the major causes of failure. The lowest value (59 mg. per cent) was obtained in a patient with acute heart failure due to rheumatic heart disease and tricuspid insufficiency. The effect of recompensation was similar to that described for serum cholesterol.

Fasting Blood Sugar. Only two patients (1 per cent), both with acute failure, had a fasting blood sugar below 60 mg. per 100 cc., while 34 per cent had a fasting blood sugar above 100 mg. per 100 cc., and 14 per cent above 130 mg. per 100 cc. Elevated fasting blood sugar was equally common in patients with acute and chronic failure. Levels above 130 mg. per 100 cc. were much more common in patients with failure due to arteriosclerosis or hypertension than to rheumatic heart disease. (Table III.)

Blood Urea Nitrogen. Azotemia occurred in 24 per cent of patients and was slightly more frequent in those with acute failure (27 per cent) than with chronic failure (21 per cent). It was more frequent in patients with right heart failure due to arteriosclerosis or hypertension than in those with rheumatic heart disease. (Table III.) There was no correlation between the occurrence of azotemia and the incidence or degree of abnormality of any of the indices of liver function.

Time Course of Alterations in Indices of Liver Function. Continuation or exacerbation of right heart failure was associated with persistence or worsening of abnormalities in indices of liver function, while compensation of the failure was followed by improvement in most of the indices. This was more striking in patients with acute decompensation, or acute exacerbation of chronic failure, than in those with chronic failure. In many patients in the former groups all indices of liver function returned to normal following compensation, except for serum globulin concentration and the cephalin-flocculation reaction. Improvement was most rapid and striking in transaminase activity and serum bilirubin concentration, which usually fell to near normal levels in one to three days and to normal within a week. Bromsulfalein retention returned to normal a little more slowly, within one to two weeks. Prothrombin concentration

TABLE III

BLOOD UREA NITROGEN AND FASTING BLOOD SUGAR LEVELS IN PATIENTS WITH RIGHT-SIDED FAILURE

Classification	Blood Urea Nitrogen		No.	(%) Patients with a Fasting Blood Sugar of		
	No.	(%) Elevated		100–130 mg./100 cc.	>130 mg./100 cc.	<60 mg./100 cc.
Acute Versus Chronic Failure						
Total patients	144	24	144	20	14	1
Acute failure	83	27	84	21	14	2
Chronic failure	61	21	60	19	14	0
According to Causes						
Arteriosclerotic heart disease	48	31	49	25	14	2
Hypertensive cardiovascular disease	30	33	29	21	24	3
Rheumatic heart disease	43	19	44	23	5	0
Miscellaneous	20	5	20	5	20	0

increased gradually during a period of two to three weeks, and serum cholesterol, cholesterol esters and cholinesterase during a period of about one month. Serum albumin concentration rose more slowly, during one or more months, and was less likely to return to normal levels. In patients with chronic failure, and in some with acute exacerbation of chronic failure, the serum bilirubin concentration and transaminase activity returned to normal following compensation, but the other indices of hepatic function usually did not return entirely to normal.

Correlation of Indices of Liver Function with Clinical Findings. The most marked difference in indices of liver function between patients with acute and chronic right heart failure was the much greater incidence and degree of elevation of serum transaminase activity, and to a lesser extent of bilirubin concentration, in patients with acute failure. The degree of these changes could be roughly correlated with the acuteness and severity of the right heart failure, as manifested by the rapidity of onset and degree of symptoms, hepatic enlargement, elevated venous pressure and hepatojugular reflux. However, there was no precise correlation with any single measurement such as the size of the liver, venous pressure or hepatojugular reflux, as these were often increased in the absence of elevated serum transaminase and bilirubin, particularly in patients with chronic failure. There was likewise no correlation with the presence or degree of left heart failure, pulmonary congestion or edema, hypotension or cyanosis. None of the patients had reduction in mean blood pressure of more than 20 mm. Hg, or clinical signs of shock, prior to estimation of hepatic function. Of five patients with SGOT activity above 200 units, three had clinical evidence of pulmonary edema or congestion with cyanosis, due to left heart failure or rheumatic mitral valvular disease, two did not have cyanosis or clinical or postmortem evidence of pulmonary change. Of twenty-five patients with SGOT activity between 40 and 200 units, five had evidence of pulmonary edema or congestion, the remainder had relatively clear lung fields on physical or roentgenographic examination. Furthermore, elevated transaminase activity and marked bilirubinemia were seldom observed in patients with severe left heart failure, pulmonary congestion or edema, hypotension or visible cyanosis when accompanying right heart failure was of mild degree or gradual in onset. Therefore it appears that the acuteness and severity of right heart failure were the most important factors in eliciting elevation of serum transaminase activity and perhaps bilirubin concentration, but that left heart failure might in some instances have contributed to more marked degrees of elevation.

The etiology of right heart failure did not appear to influence the pattern of alterations in

indices of hepatic function as much as the difference between acute and chronic failure. Patients with hypertensive heart disease had a slightly higher incidence of acute failure and transaminase elevation than those with other forms of heart disease. Patients with rheumatic heart disease, who had a greater frequency of attacks of failure over a prolonged period of time, had a somewhat higher incidence of abnormal serum bilirubin and globulin levels and positive cephalin flocculation tests, and, to a lesser extent, of depressed serum albumin, cholesterol and cholesterol esters. (Table II.)

Correlation of Indices of Liver Function with Histologic Change in the Liver. The liver was examined histologically in sixteen patients postmortem and in biopsy specimens obtained in three. Fourteen patients were classified as having acute failure, five chronic failure. All the patients with acute failure had evidence of hyperemia and congestion of the central zone of the hepatic lobules, and half the patients had significant necrosis of liver cells. This was most marked in the central zone, which contained pyknotic nuclei, cell fragments, polymorphonuclear leukocytes and red blood cells. All seven patients with centrilobular hepatic necrosis had increased serum transaminase activity and bilirubin concentration, and there was a rough correlation between the degree of these changes. The patients with hepatic necrosis included three with rheumatic heart disease, two with constrictive pericarditis and two with arteriosclerotic heart disease. All had right heart failure of acute onset and severe degree; in three this was the initial episode of failure and in the remainder it was an acute exacerbation of chronic failure. Only three patients had left heart failure or pulmonary congestion of sufficient severity to cause pulmonary edema, and only one had clinical evidence of shock for several hours before tissue was obtained for examination. None of the patients with acute right heart failure without significant hepatic necrosis had elevated transaminase activity. These patients included three with rheumatic heart disease, three with arteriosclerotic heart disease, and one with cor pulmonale.

None of the five patients who had been classified as having chronic failure had either significant hepatic necrosis or elevation of serum transaminase activity. These included two patients with constrictive pericarditis, one with arteriosclerotic heart disease, one with cor pulmonale, and one with congenital heart disease. All had a varying degree of fibrosis, usually extending from the center of the hepatic lobules but in some instances also involving the periportal areas. Some also had hyperemia and congestion of the central zone of the hepatic lobules. The patients with acute exacerbation of chronic failure had similar fibrotic and congestive changes. In most patients with hepatic fibrosis the changes varied from early to more marked fibrous proliferation, suggestive of several previous bouts of failure.

Except for the association of elevated serum transaminase activity and moderate bilirubinemia with centrilobular necrosis, no strict correlation could be made between alterations in indices of liver function and histologic changes. Alterations in bromsulfalein retention, in concentration of serum globulins, albumin, prothrombin, cholesterol and cholesterol esters, and in the cephalin-flocculation reaction and cholinesterase activity occurred both in patients with and without hepatic congestion, necrosis or fibrosis. Patients with more marked hepatic fibrosis, particularly those with rheumatic heart disease or constrictive pericarditis, tended to have a greater degree of change in serum globulins, albumin and prothrombin concentration, and in the cephalin flocculation test. However, even in patients with sufficient fibrosis and regeneration to be classified as cardiac cirrhosis there were no chemical findings distinct from those seen in congestive hepatomegaly or mild fibrosis.

COMMENTS

Acute or chronic right heart failure resulted in a high incidence of alteration of all parameters of liver function that were studied, including those measuring primarily excretory function (serum bilirubin, bromsulfalein retention and alkaline phosphatase activity), those reflecting mainly cell destruction (SGOT and SGPT activity), those reflecting production of abnormal proteins (serum globulin and thymol turbidity), and those reflecting decreased biosynthesis (serum cephalin flocculation, plasma prothrombin concentration, serum albumin, cholinesterase activity, cholesterol and cholesterol esters). No one group of liver functions was affected out of proportion to the others, and the functions within each group were affected in varying frequency and degree. As in many other disorders of the liver, bromsulfalein retention

was the most sensitive index of function. Prothrombin concentration was depressed in the same proportion of patients (80 per cent), but the degree of change was usually less marked. The next most frequently altered index of liver function was the serum globulin concentration (elevated, usually to a slight degree, in 51 per cent of the patients). Depression below normal values occurred with somewhat less frequency in the following indices: serum cholinesterase (48 per cent), serum cholesterol (46 per cent), cholesterol esters (37 per cent), and serum albumin (30 per cent), but these alterations were usually not marked. Serum bilirubin concentration and SGOT activity were increased in 31 and 33 per cent, respectively, and the degree of change was frequently pronounced in patients with severe acute right heart failure. Alterations in other indices of liver function were less frequent, the cephalin-flocculation test being positive in 19 per cent, SGPT activity increased in 11 per cent, alkaline phosphatase increased in 10 per cent, and the thymol turbidity test positive in 2 per cent.

The pattern of altered liver functions was the same in acute and chronic right heart failure except that the former showed a much higher incidence and degree of elevation of SGOT and SGPT activity, and to a lesser extent of serum bilirubin concentration. The elevation of serum transaminase activity could be correlated with the acuteness and severity of right heart failure and with the presence and extent of centrilobular necrosis in the liver, and appeared to be due mainly to the destruction of liver cells. The other indices of liver function showed abnormalities slightly more often and to a slightly greater degree in acute than chronic failure, but the differences were much less marked. Except for the association of increased serum transaminase activity and of moderate or marked bilirubinemia with right heart failure of acute onset and severe degree, and with centrilobular necrosis, there was no precise correlation of any of the indices of liver function with the clinical manifestations of right heart failure (elevated venous pressure, hepatojugular reflux, hepatomegaly, splenomegaly, edema or ascites) or with left heart failure, alteration in systemic blood pressure, or histologic changes in the liver (congestion, necrosis, fibrosis or cirrhosis). There was likewise no precise correlation with the etiology of heart failure, although patients with hypertensive heart disease had a somewhat higher incidence of acute failure and of transaminase elevation, and patients with rheumatic heart disease had a higher incidence of recurring failure, decreased biosynthetic activity of the liver, and hyperglobulinemia.

The alterations in indices of liver function observed are in general similar to those reported by many others (Table IV), except for the higher incidence of elevated serum transaminase activity observed in acute right heart failure. Alterations in hepatic function occurring in congestive heart failure have been attributed mainly to anoxemia [*4,5,23*]. The liver cells at the center of each lobule receive blood at lower oxygen tension than those at the periphery, and are believed to be more susceptible to reduction of oxygen tension in the hepatic venous blood. Most patients with right heart failure do not have reduction in arterial oxygen tension but do have a marked unsaturation of hepatic venous blood [*5,23*]. The precise role of increased venous pressure, reduced hepatic blood flow and reduced cardiac output is not known. Ingelfinger [*24*] has demonstrated reduced hepatic blood flow in patients with congestive heart failure, with a resultant marked decrease in the rate of liver cell activity.

The histologic alterations of the liver in right heart failure have been well described [*4,25–27*], and include dilatation of the central veins, engorgement of sinusoids and, in severe cases, hemorrhage from sinusoids and focal centrilobular necrosis. The latter change was observed mainly in patients with right heart failure of acute onset and severe degree, and while it appears to be the result of acute hepatic congestion and anoxemia, the mechanism is not clear. There was no precise correlation with degree of venous pressure elevation, hepatojugular reflux or hepatomegaly, and in only one patient could shock, a common cause of centrilobular necrosis [*25*], be implicated. Sherlock [*4*] could find no correlation between the extent of hepatic cell necrosis in congestive heart failure and the degree of elevation of venous pressure or reduction in cardiac output or arterial oxygen saturation.

Following recovery from a bout of decompensation, fibrosis occurs in the centrilobular areas. With repeated bouts of failure, the fibrosis may extend toward the portal areas and there may be nodular regeneration of liver cells, although not as marked as in Laennec's cirrhosis. Cirrhosis due to cardiac failure is

uncommon, occurring in only 4 to 10 per cent of patients dying with right heart failure [*28,29*]. The physical findings in congestive hepatomegaly without cirrhosis may be the same as in cardiac cirrhosis, including the occurrence of ascites and splenomegaly, and similar alterations in hepatic function may occur in both. Cardiac cirrhosis can be diagnosed only by histologic examination of the liver, although the finding of a small liver, or progressive reduction of liver size, in the presence of continued ascites and splenomegaly, may suggest the diagnosis. The observations in the group under study confirm reports of Sherlock [*4*] and of Koletsky and Barnebee [*27*] that in the great majority of patients with right heart failure functional impairment of the liver is due to hepatic congestion and probably anoxia rather than to cirrhosis. The rapid improvement in hepatic function that occurred in almost all instances following compensation of heart failure also supports this finding.

Indices of Excretory Function. Bilirubin: Increased serum bilirubin concentration occurring in right heart failure has been generally attributed to impaired excretion due to hepatic anoxemia [*30–32*]. In most patients with mild bilirubinemia who were studied there was no alteration in serum transaminase activity, but in those with more marked jaundice there was concomitant elevation in serum transaminase, often to high levels. With continued decompensation, or with correction of the heart failure, the serum bilirubin and transaminase activity changed concomitantly. This suggests that marked elevation in serum bilirubin occurring in patients with acute right heart failure may be due, at least in part, to centrilobular hepatic necrosis.

While pulmonary infarction can, if present, contribute to the presence of bilirubinemia, clinical jaundice was repeatedly observed in patients with right heart failure in whom there was no postmortem evidence of pulmonary, splenic, renal or other infarction. An early report that the presence of pulmonary infarction is indispensable to clinical jaundice in patients with congestive heart failure [*33*] has been amply disproved [*34,35*].

Bromsulfalein Retention. The excretion of injected bromsulfalein is a measure of hepatic blood flow [*36–38*] and of the capacity of the liver cells to conjugate the dye, a function which is markedly impaired by anoxia [*39*]. Bromsulfalein

TABLE IV

PER CENT INCIDENCE OF ABNORMALITY OF INDICES OF LIVER FUNCTION IN PREVIOUS STUDIES ON CONGESTIVE HEART FAILURE

Author	Total No. of Patients	Excretory			Cell Destruction		Abnormal Proteins		Biosynthetic Functions					
		Bilirubin	BSP	Alkaline Phosphatase	SGOT	SGPT	Globulins	Thymol Turbidity	Cephalin Flocculation	Prothrombin Time	Albumin	Cholinesterase	Cholesterol	Cholesterol Esters
Jolliffe [*1*]	16	81	75	...	...	...	...	...	...	...	...	...	...	...
Cantarow [*8*]	42	24	33	...	...	...	...	...	...	...	...	...	...	...
Chavez [*9*]	30	100	...	...	...	...	...	...	...	...	...	...	...	...
Anderson [*92*]	142	...	...	...	...	...	...	...	...	16*	...	...	...	...
Ernst [*80*]	27	...	...	...	...	...	...	26	...	...	...	...	...	...
Stillerman [*81*]	56	...	...	...	...	...	...	48	...	...	...	...	...	...
Felder [*6*]	149	52	85	43	...	...	...	31	22	...	...	...	55†	...
White [*2*]	30	39	57	...	...	...	42	...	32	...	28	...	28	33
Sherlock [*4*]	50	68	...	...	...	...	23	37	27	...	63	...	37	...
Evans [*5*]	105	26	96	...	...	...	...	6	...	54‡	...	...	...	...
Bjerkelund [*7*]	35	52	...	...	...	...	34	11	37	90	...	...	...	21
White [*3*]	75	40	78	17	0	...	...	...	...	...	...	...	...	...
Denney [*54*]	10	...	...	...	0	...	...	...	...	...	...	...	...	...
Kessler [*55*]	46	...	...	...	21	...	...	...	...	...	...	...	...	...
Lieberman [*99*]	14	...	...	...	0	...	...	...	...	...	...	...	...	...
Chinsky [*56a*]	26	...	...	...	25	...	...	...	...	...	...	...	...	...
Fragge [*63*]	24	...	...	...	...	...	...	...	...	...	...	...	...	...
Present study	175	31	80	10	33	11	51	2	19	80	30	48	46	37

* Values below 50 per cent of normal. † 55 per cent (rheumatic heart disease), 28 per cent (not rheumatic heart disease). ‡ Values below 70 per cent of normal.

retention was the most sensitive index of hepatic dysfunction in patients with acute or chronic heart failure, as has been previously observed [*5,6,40*]. Marked retention was more common in acute than chronic failure, but there was no correlation with histologic changes in the liver; while marked retention occurred in patients with hepatic necrosis and elevated serum transaminase activity, similar functional change occurred in patients with hepatic congestion or fibrosis and normal transaminase activity.

Alkaline Phosphatase. The origins and factors influencing serum alkaline phosphatase activity are not entirely clear. In the adult, normal enzyme activity indicates integrity of the excretory biliary channels, both intrahepatic and extrahepatic, since obstruction results in an increase of activity [*41,42*]. Chronic infiltrating diseases of the liver may produce elevation of serum alkaline phosphatase in the presence of normal serum bilirubin concentration [*43*]. In patients with congestive heart failure, the incidence of elevation of serum alkaline phosphatase activity was low (10 per cent) and there was no correlation with histologic changes in the liver such as centrilobular congestion, necrosis, fibrosis or cirrhosis. In patients with elevated serum transaminase activity, there was a normal or occasionally a falling level of alkaline phosphatase despite increasing jaundice, a relationship similar to that frequently observed in hepatocellular disease [*44*]. The highest values of serum alkaline phosphatase activity occurred in patients with an enormously distended liver, in whom the extreme congestion may have caused some intrahepatic obstruction.

Indices of Cell Destruction. SGOT and SGPT: Serum transaminase activity increases when hepatic necrosis occurs as a result of hepatitis [*45,46*], hepatotoxic agents [*47*] or other causes. Whether or not the SGPT activity is a more sensitive index of hepatocellular necrosis than the SGOT still is a matter of dispute. Sherry [*48*] believes that SGPT is not a uniformly more specific index of hepatic necrosis, whereas others [*49–52*] found the SGPT to exceed the SGOT. In patients with acute right heart failure and elevated transaminase, SGOT was found to be increased more frequently and to a greater degree than SGPT.

In the patients with right heart failure who were studied, elevated serum transaminase activity was observed primarily in those with failure of acute onset and severe degree, and was rarely seen in chronic failure. It was accompanied by centrilobular liver cell necrosis in all patients in whom histologic examination of the liver could be made, and in no instance was there significant liver cell necrosis in the absence of elevated serum transaminase activity. These observations suggest that the elevated transaminase activity observed in acute right heart failure is primarily due to liver cell necrosis. However, the reported incidence of this histologic change in right heart failure [*2,4,29,74,75*] is lower than the observed incidence of SGOT elevation. Therefore, it is possible that some rise in transaminase may occur following hepatic injury insufficient to produce widespread necrosis, although such an association was not observed.

Earlier studies in patients with congestive heart failure reported normal serum transaminase activity [*53–58*], but more recently a number of reports of elevated transaminase activity have appeared, and there have been some instances of centrilobular liver cell necrosis [*50,59–64*]. However, opinion has been divided regarding the incidence and cause of these alterations in patients with congestive heart failure. None of the previous reports has indicated an incidence of SGOT elevation as high as 48 per cent in acute right heart failure. Most reports have attributed centrilobular necrosis and elevated serum transaminase observed in patients with heart failure to forward failure and reduced cardiac output and hepatic blood flow [*57,64*], since these changes were observed not only in right heart failure [*63,64*] but also in left heart failure [*63*] and in rapid arrhythmias [*57*] or myocardial infarction with hypotension, in some instances without right sided decompensation [*64*]. In the patients studied these alterations frequently occurred as a result of acute, severe right-sided heart failure, in the absence of hypotension, shock, left heart failure or pulmonary edema. Cardiac output is usually reduced in congestive heart failure, but the lack of consistent alteration in blood pressure makes it unlikely that this change was sufficiently great to cause the observed hepatic necrosis and elevated serum transaminase activity. Hence, while left heart failure [*62*] or hypotension [*63*] may under some circumstances contribute to the development of these alterations, right heart failure alone produced more marked changes and appeared to be the most important mechanism in the patients studied. A similar interpreta-

tion has been offered by Bang et al. [*62*]. However, while these authors attributed centrilobular necrosis to an acute episode of right heart failure occurring in the presence of chronic failure, the current study demonstrated centrilobular necrosis in both the initial attack of failure and in acute exacerbation of chronic decompensation. Acute congestion of the liver produced in experimental animals by partial occlusion of the thoracic inferior vena cava is known to result in centrilobular necrosis [*65*].

Further evidence suggesting that the observed increases in serum transaminase activity were due to acute right heart failure rather than to reduced cardiac output is provided by the concomitant increase that occurred in serum bilirubin concentration, often to high levels. While either acute hepatic congestion or shock may cause centrilobular hepatic cell necrosis [*25,66*], only the former would uniformly cause hyperbilirubinemia of the degree observed. Serum transaminase activity and bilirubin concentration increased with exacerbation of right heart failure, and improved rapidly with compensation. The SGOT activity, and to a lesser extent the SGPT, appear to provide a useful index of the presence, degree and duration of centrilobular necrosis in patients with acute right heart failure, and should facilitate study of the relationship of this process to the development of hepatic fibrosis and cirrhosis.

The increase in serum transaminase activity that may occur in patients with myocardial infarction as a result of centrilobular liver cell necrosis due to acute right heart failure, or possibly shock [*64*], must be differentiated from the increase in serum enzyme arising from cardiac tissue. An increase in SGPT activity approaching that of SGOT is likely to arise from the liver, as the content of SGPT in cardiac tissue is relatively low [*48,50*]. Persistence of elevated serum transaminase activity for more than forty-eight hours, or elevation above 300 units, is seldom due to myocardial infarction alone, and would suggest accompanying liver cell necrosis. When SGOT activity is above 300 units due to myocardial infarction alone, death is likely within a short period of time [*67*].

Pulmonary infarction presents less of a problem in differentiation, as transaminase values are normal in association with most infarctions [*68,69*], and when elevations do occur they rarely exceed 100 units [*70,71*]. Rheumatic carditis may cause an elevation of serum transaminase, but peak values above 200 are rare in the absence of right heart failure [*72*]. Some of the transaminase elevations originally ascribed to rheumatic carditis have been found to be due to toxic hepatitis resulting from salicylate poisoning [*73*], and some are no doubt due to hepatic necrosis resulting from acute right heart failure. Prompt reduction in elevated transaminase activity with compensation of heart failure indicates the source of the increase.

Indices of Abnormal Protein Production. Globulins: Hyperglobulinemia, usually mild, was observed in a high proportion of patients with right heart failure, particularly those with acute failure or acute exacerbation of chronic decompensation. Increase in gamma globulins is among the first chemical alteration to occur in other liver diseases [*76*], and is reported to be a sensitive indicator of early liver disease [*77*]. Since hyperglobulinemia was not more marked in patients with elevated transaminase activity, the increase herein noted does not appear to be related to hepatic cell necrosis.

Thymol Turbidity. Increased thymol turbidity occurring in patients with liver disease has been attributed to an increase or alteration in the gamma globulin and other serum protein fractions [*78*]. This test is generally less sensitive than the cephalin flocculation test, and usually occurs later in the course of hepatic disease [*79*]. Only 3 per cent of patients with acute right heart failure, and none of those with chronic failure, had increased thymol turbidity. This incidence of abnormality in congestive heart failure is lower than previously reported [*80,81*]. The lack of any elevation in patients with increased transaminase activity indicates that hepatic necrosis alone does not produce the alteration in plasma proteins responsible for increased thymol turbidity.

Indices of Biosynthetic Functions. None of the indices reflecting synthesis by the liver appeared to be altered to a greater degree in patients with increased transaminase activity than in those with normal transaminase, with the possible exception of serum cholesterol and cholesterol ester concentration. While hepatic necrosis would be expected to result in decreased synthesis by the liver, the life span in the blood of the substances synthesized is sufficiently long to mask variations in production of short duration, such as might be associated with acute hepatic necrosis. In patients who survived repeated

episodes of acute right heart failure more severe alterations in these functions did develop.

Cephalin-Flocculation Reaction. The gamma globulin component of serum normally fails to cause flocculation of cephalin-cholesterol emulsions in man, because of the inhibitory action of substances, possibly alpha globulins, in the electrophoretically separated albumin fraction [*82*]. These stabilizing substances disappear from the serum within forty-eight hours following acute parenchymal liver injury [*78*]. A positive cephalin-flocculation reaction has been reported to occur in from 20 to 89 per cent of patients with right heart failure [*81,83–85*], the highest incidence being found in failure due to rheumatic heart disease [*81,84*]. In the patients studied, a positive cephalin-flocculation test was obtained in 19 per cent of those with right heart failure, and in 39 per cent of those with failure due to rheumatic heart disease. The increased incidence in patients with rheumatic heart disease may be due to more repeated episodes of failure and a higher incidence of cardiac cirrhosis [*27,86*]. As with the thymol-turbidity reaction, there was no correlation of the results of the cephalin-flocculation test with increased serum transaminase activity, indicating that hepatic necrosis alone is not responsible for a positive reaction.

Albumin. Albumin is synthesized in the liver [*87*], and hypoalbuminemia is a good index of chronic liver disease [*79*], including that due to chronic right heart failure [*5,88,89*]. The lowest values are found in patients with prolonged failure, particularly in those in whom cardiac cirrhosis develops [*89*]. It is of interest that hypoalbuminemia occurred in only 30 per cent of patients with either acute or chronic failure, and was usually of moderate degree. Since the life span of serum albumin is approximately one month [*90*], it is not surprising that acute hepatic necrosis and elevated transaminase levels were not associated with further reduction in serum albumin. With compensation of heart failure, improvement in hypoalbuminemia occurred over a period of one or more months in about half the patients.

Prothrombin Concentration. Plasma prothrombin, which is produced by the liver in the presence of vitamin K [*91*], has been reported to be reduced in 20 to 90 per cent of patients with heart failure [*3,7,92,93*]. In the patients with right heart failure studied the prothrombin concentration was reduced in 80 per cent, an incidence equal to that of bromsulfalein retention, although the degree of change was usually less marked. Hence, prothrombin formation is a sensitive index of hepatic dysfunction due to heart failure. While the degree of change was seldom sufficient to cause bleeding, it is well known to cause increased reactivity to coumarin drugs. The prothrombin concentration was not lower in patients with elevated transaminase activity. Compensation of failure was usually followed by a gradual increase in prothrombin concentration, more rapidly and to a greater degree than in the case of serum albumin.

Cholinesterase. Plasma cholinesterase is produced by the liver and is reduced following hepatocellular injury, as well as in many acute and chronic illnesses which may affect the liver only indirectly [*94*]. The life span of this protein in the blood is approximately the same as that of serum albumin, and alteration in cholinesterase activity frequently parallels that of serum albumin, although reduction in the former may occur more rapidly. Serum cholinesterase activity was reduced in approximately half the patients with right heart failure who were studied, and alterations in enzyme activity occurred more rapidly with exacerbation and compensation of right heart failure than in the case of serum albumin concentration.

Cholesterol and Cholesterol Esters. The liver is the primary site of cholesterol production [*95–97*] and esterification [*98*]. In congestive heart failure, serum cholesterol and cholesterol esters have been found to be decreased in from 21 to 55 per cent of patients [*2,6*]. In the patients studied, a decreased concentration occurred in 46 and 37 per cent, and was more marked in those with acute failure. In the latter, the serum cholesterol concentration usually returned towards normal following recompensation while in those with chronic failure the cholesterol level was more refractory to improvement. The greatest depression of cholesterol and cholesterol esters occurred in patients with markedly elevated transaminase activity, indicating that cholesterol biosynthesis may have been acutely affected by centrilobular necrosis.

Fasting Blood Sugar. Hypoglycemia has been reported to occur in patients with severe chronic congestive heart failure, and to cause episodes of disordered behavior which can be relieved by the administration of glucose [*99*]. It has been postulated that these episodes of hypoglycemia are hepatic in origin. In the patients studied, hypoglycemia was noted in only 1 per cent, although it is likely that more frequent deter-

mination of fasting blood sugar may have disclosed additional transient reductions. Hyperglycemia was much more frequently observed. Mild elevations of fasting blood sugar in the range of 100 to 130 mg. per cent usually returned towards normal within one to two days after compensation of the failure, and may have been due to a "stress" response. Elevations above 130 mg. per cent usually persisted, and were of approximately the same frequency as in the general hospital population. There was no alteration of the fasting blood sugar that could be related to hepatic cell necrosis or elevated serum transaminase activity.

SUMMARY

Serial liver function tests were performed in 175 patients with right-sided heart failure of diverse etiology. The cases were classified as acute or chronic depending on the duration and severity of congestive failure. The indices of liver function studied and the incidence of abnormal values obtained were as follow. *Excretory function:* serum bilirubin (31 per cent), bromsulfalein retention (80 per cent), alkaline phosphatase (10 per cent). *Parenchymal cell destruction:* serum glutamic oxalacetic transaminase (33 per cent), serum glutamic pyruvic transaminase (11 per cent). *Abnormal serum protein production:* serum globulins (51 per cent), thymol turbidity (2 per cent). *Biosynthetic functions:* plasma prothrombin concentration (80 per cent), serum albumin (30 per cent), cephalin flocculation (19 per cent), cholinesterase activity (48 per cent), cholesterol (46 per cent), cholesterol esters (37 per cent).

The causes of the right heart failure did not appear to influence the pattern of altered liver function as much as whether failure was acute or chronic. The liver indices reflecting parenchymal cell destruction and excretory activity were most affected during acute failure. Elevated levels of transaminase (up to 1,200 units) and bilirubin (up to 8 mg. per cent) were obtained in half of the patients with acute failure, in the absence of myocardial or pulmonary infarction. A much greater incidence of elevated transaminase levels was found in acute failure (49 per cent) than in chronic failure (5 per cent). These changes correlated with the presence of centrilobular hepatocellular necrosis.

The majority of indices of hepatic function returned to normal within one to two weeks following cardiac compensation, except for those reflecting biosynthesis by the liver, which improved more slowly, and hyperglobulinemia, which tended to persist. Repeated attacks of failure (as in rheumatic heart disease) were associated with more severe impairment in liver function.

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Whipple's Disease*

A Review of Twelve Patients from One Service

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Over one hundred cases of intestinal lipodystrophy have been reported since the original description by Whipple in 1907 [*1*]. While the diagnosis is open to question in some of these patients, it has been well documented in most of them by appropriate staining of intestinal mucosa or lymph nodes. In the past decade more than fifty cases have been reported, and it is clear that the disease is far more prevalent than it was thought to be. It is being recognized during life in more and more cases, and a clinical diagnosis has been made in many patients before biopsy. In the past, patients having Whipple's disease usually have declined steadily and died within a few months or years after the onset of their illness. However, since 1952, twelve patients [*2–13*] have been reported on who responded to therapy and who were surviving at the time of publication.

Table I
GENERAL DATA

Case No.	Age (yr.)* Race and Sex	Duration of Symptoms†	Year of Diagnosis	Mode of Diagnosis‡	Survival Following Diagnosis (mo.)	Present Status
I	35, W, M	19	1936	A	. . .	Dead
II	52, W, M	12	1940	A	. . .	Dead
III	45, W, M	12	1944	A	. . .	Dead
IV	55, W, M	9	1944	MLN	5	Dead
V	58, W, M	14	1949	MLN	10	Dead
VI	56, N, M	12	1950	MLN	1	Dead
VII	62, W, M	48	1954	MLN	72	Alive
VIII	47, W, M	11	1954	MLN	77	Alive
IX	39, W, M	6	1955	MLN	55	Alive
X	53, W, M	36	1957	PLN	3	Dead
XI	47, W, M	7	1959	IM	12	Alive
XII	48, W, F	6	1959	IM	6	Alive

* At the time of diagnosis.
† (Excluding arthralgia) in months before diagnosis.
‡ A indicates autopsy; MLN indicates mesenteric lymph node; PLN indicates peripheral lymph node; IM indicates intestinal mucosa (peroral).

Our changing concept of this disorder and the possibility of diagnosis during life, the fact that remission may follow appropriate therapy and that the disease is not necessarily fatal, have led us to review twelve proved cases of Whipple's disease seen here during the past twenty-four years.

MATERIAL

Of these twelve patients, eight have been reported on previously [*13–17*]. The ages of the patients at the time of diagnosis ranged from thirty-five to sixty-two years. (Table I.) All were white except one who was reported by all observers to be a Negro. Investigation of his family records would indicate that probably he was part Indian. There were eleven men and one woman in this series. The diagnosis was established by autopsy in three patients, by laparotomy in six, by biopsy of a peripheral lymph node in one and by peroral intestinal biopsy in two. In six of these cases clinical diagnoses were obtained prior to tissue confirmation. Five of the twelve patients were alive and well at the time of this report.

SYMPTOMS

The characteristic syndrome of intermittent arthralgia, abdominal pain, diarrhea, weight loss, lymphadenopathy and impaired intestinal absorption was seen in most of these patients. (Tables II, III and IV.)

The arthralgia was migratory, affecting either large or small joints. It was noted in every case and antedated abdominal symptoms in all but one. Episodes of acute inflammation of the joints with objective changes were observed in two patients. In four patients a recrudescence of arthralgia often accompanied a recurrence of abdominal symptoms.

Vague, postprandial distress and eructation were among the most prevalent complaints and

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TABLE II
SYMPTOMS

Case No.	Weight Loss (lb.)	Arthralgia	Abdominal Pain	Nausea and Vomiting	Diarrhea	Average Stools per Day	Chills and Fever	Melena
I	59	+	+	+	+	3–6	+	+
II	55	+	+	+	+	10–12	+	0
III	75	+	+	+	+	18–20	0	0
IV	100	+	0	+	+	5–6	+	0
V	60	+	+	0	+	5–10	+	0
VI	35	+	+	+	0	1	+	+
VII	65	+	+	+	+	8–12	0	0
VIII	23	+	+	+	+	8–10	0	0
IX	20	+	+	0	0	0–1	+	0
X	64	+	+	+	+	6–8	0	0
XI	37	+	+	+	0	0–1	+	0
XII	42	+	+	+	+	15–20	+	0

TABLE III
PHYSICAL FINDINGS

Case No.	Blood Pressure (mm. Hg)	Lymphadenopathy	Fever	Heart Murmur	Skin Pigmentation	Abdominal Tenderness	Abdominal Mass
I	102/60	+	+	0	0	+	0
II	76/30	+	+	+	0	+	0
III	95/62	0	0	0	0	0	0
IV	100/60	+	+	+	+	+	0
V	100/50	+	+	+	+	0	0
VI	90/50	+	+	0	0	+	+
VII	124/60	+	0	+	+	+	+
VIII	120/70	0	0	0	+	0	0
IX	106/70	0	0	0	0	+	+
X	90/55	+	0	+	0	0	0
XI	110/60	0	+	0	+	+	0
XII	110/70	0	+	0	0	+	0

TABLE IV
LABORATORY FINDINGS

Case No.	Hematocrit (vol. %)	Sedimentation Rate (mm./hr.)	Serum Albumin (gm./100 ml.)	Serum Globulins (gm./100 ml.)	Serum Calcium (mg./100 ml.)	Serum Cholesterol (mg./100 ml.)	Serum Carotene (μg./100 ml.)	Serum Vitamin A (μg./100 ml.)	Occult Blood in Stool	Fat Malabsorption	Abnormal Roentgenogram of the Small Intestine
I	35	...	2.8	2.7	8.6	...	...	...	+	...	+
II	28	28	2.4	3.2	7.0	...	...	...	+	+	...
III	32	26	3.6	2.2	...	...	16	38	0	...	...
IV	26	32	1.0	3.1	6.5	44	28	85	+	+	+
V	24	34	2.2	3.7	5.5	100	15	16	+	+	+
VI	25	18	2.4	4.3	7.4	90	22	16	0	...	+
VII	26	...	2.9	3.3	7.4	100	13	22	0	+	+
VIII	39	21	4.2	2.6	8.5	137	34	37	+	+	+
IX	34	64	...	...	...	80	...	...	0	0	+
X	40	15	2.6	2.5	8.2	129	14	...	...	+	+
XI	24	34	2.4	4.2	7.5	256	...	...	0	+	+
XII	30	...	3.7	2.1	8.1	...	...	...	0	+	+

were usually the first abdominal symptoms to appear. Episodes of anorexia, nausea and vomiting were common. Cramping or colicky abdominal pain, periumbilical or epigastric in location, ultimately appeared in all cases but one. Intermittent, watery diarrhea was present in nine patients, and five had frank steatorrhea. In general, once diarrhea became prominent, the course was steadily downhill. In the patients who died, survival after the onset of diarrhea ranged from three to fifteen months. It is important to note, however, that three patients had no diarrhea at any time during the course of their illness. Melena was reported by two patients and in one case massive gastrointestinal hemorrhage was observed during hospitalization.

Weight loss was reported in every patient, varying between 20 and 100 pounds. However, even in the fatal cases remissions with a gain of a few pounds in weight were seen occasionally. Intermittent chills and fever occurred in eight patients, and two had night sweats. Non-productive cough and dyspnea were also noted in a few cases. Two patients had multiple bone fractures during their illness.

PHYSICAL FINDINGS

The most striking physical findings in these cases was the appearance of chronic illness and emaciation. Dehydration was common. Fever was observed in seven patients; it rarely exceeded 102°F., except as a terminal event. Discrete, non-tender axillary, cervical or epitrochlear lymph nodes were present in seven patients.

Distention and diffuse tenderness were the most common abdominal signs. In three cases abdominal masses in the epigastric or left hypochondriac regions were palpated. The liver and spleen were enlarged in only one patient in whom hepatitis was found at autopsy. At proctoscopy, erythema, edema and friability of the mucosa were noted in two cases, but no significant abnormalities were found in the other six patients examined.

Cardiac enlargement was noted only in the terminal phase, and in no patient was a pericardial rub heard. However, aortic systolic and diastolic murmurs were heard in one patient, who had bacterial endocarditis and aortic valvular vegetations at autopsy, and an aortic diastolic murmur was a transient finding in one patient, who still survives. A diastolic murmur was also noted in another patient. Systolic murmurs were present in five patients including one who was found at autopsy to have bacterial endocarditis involving the tricuspid valve. In one patient no murmur was heard though bacterial endocarditis and vegetations on the mitral valve were found on postmortem examination. Most patients had a significant hypotension. Increased pigmentation of the exposed areas of the skin ultimately appeared in five cases. Three patients had edema as a terminal manifestation.

LABORATORY FINDINGS

With one exception every patient in whom appropriate tests were made showed impairment of fat absorption. The vitamin A tolerance test curves were flat in three cases. An increased fecal fat was noted by microscopic stool examination in five. In two patients the fecal fat was 56 and 59 per cent, respectively, of the dry weight. Fat balance studies were obtained on two occasions in one patient, averaging 32 and 36 gm. per day. I^{131}-labeled triolein studies were performed in five patients. There was marked impairment of absorption in three, moderate impairment in one, and the remaining patient had normal values. Two of the patients with marked impairment had a complete clinical remission following treatment, during which results of the I^{131}-labeled triolein tests returned to normal. Glucose tolerance test curves were flat in three cases and normal in four. The serum cholesterol levels were depressed in seven of eight patients in whom the determination was made, as were the plasma carotene values in all seven patients tested, the latter reflecting impaired intestinal absorption of many months' duration [*18*]. The fasting plasma vitamin A ranged from 5 to 37 μg. per 100 ml. in the six patients in whom it was measured.

The feces was observed to be pale and foamy in four patients. Results of a chemical test of the feces for blood was positive on repeated occasions in five patients.

A hypochromic, microcytic anemia usually was present, the lowest observed hemoglobin concentrations in the various cases ranging from 6.2 to 11.8 gm. per 100 ml. In the five patients who still survive, and during a remission in one fatal case, the hemoglobin values returned to normal. A slight reticulocytosis was usually present, and bone marrow aspirations in seven patients revealed increased cellularity in five and an increase in plasmatocytes in three.

Leukocytosis was infrequently noted. Only five patients had counts of over 12,000 per cu. mm. at any time while under observation, and in these four there were no counts over 16,000 per cu. mm. prior to the terminal phase. The erythrocyte sedimentation rate was invariably elevated. Eosinophilia was very infrequent, being significant in degree in only two of the many blood counts performed on the twelve patients.

Roentgenographic examination revealed an abnormal small intestine in ten cases. The findings consisted of thickening or coarsening of the mucosal folds, segmentation, dilatation and hypomotility, and flocculation. In two cases displacement of the upper abdominal viscera suggested the presence of a retroperitoneal mass. The barium enema revealed no abnormalities in the nine cases in which this examination was performed. Other roentgenographic findings included pleural thickening or effusion in three cases and increased bone translucency in four.

One patient had repeatedly positive results of urine tests for Bence Jones protein. Results of studies of the marrow for myeloma cells were negative. Although pyuria and proteinuria of slight degree were usually present, evidence of severe renal disease was lacking in all but one patient, who died in uremia and was found at autopsy to have interstitial nephritis. Marked derangements in serum electrolytes were not noted. Two patients exhibited slight hyponatremia, and one had moderately severe hypokalemia. The electrocardiogram revealed non-specific S-T segment and T-wave changes in three cases and was normal in three other patients.

Other laboratory findings are shown in Table IV. The serum albumin, serum calcium and serum cholesterol values were usually low and, in general, correlated with the degree of malnutrition. The serum globulins were elevated in three cases.

ANATOMIC FINDINGS

The pathologic changes observed at laparotomy or autopsy were those now recognized as characteristic of Whipple's disease. The peritoneal surfaces were often dull, grey and roughened, and fibrinous adhesions were present in a few cases. Small amounts of clear, straw-colored peritoneal fluid were noted in four cases, but chylous ascites was not found. Dilatation of the small intestine and increased thickness and rigidity of the bowel wall were usually observed, together with grey, fuzzy fibrinous exudate on the mucosa. The mucosa was often found to be darkly discolored and interspersed with yellow flecks. The flecks proved to be the enlarged villi which were distorted by collections of large macrophages and by fat-filled spaces above the lamina propria and beneath the epithelium. Focal mucosal hemorrhages were noted frequently.

The extent of involvement of the bowel in the inflammatory process was quite variable. Thus in two cases there was an inflammatory reaction composed of large mononuclear cells diffusely involving the entire small intestine. In another, involvement was confined to the jejunum, while in the remaining two cases both the small bowel and the colon were inflamed throughout their entire length.

The mesentery was thickened, and in every case there was generalized enlargement of the mesenteric, periaortic and celiac lymph nodes, with diameters as great as 6 cm. The lacteals were found to be dilated in two cases at laparotomy but were non-contributory in the cases at autopsy. The thoracic duct was explored and was patent in two cases.

The lymph nodes had a pasty yellow color, paler than usual, and a sieve-like appearance on cross section. In some cases there was only minimal alteration of the lymph nodes with a slight increase in the number of macrophages scattered in the lymphoid and reticular areas, but in other cases there was marked involvement with alteration of the entire architecture and replacement of the usual structure by large, fat-containing spaces which were often surrounded by giant cells. Around and between these spaces were numerous large macrophages and, sometimes, small epithelioid cell granulomas. Groups of foam cells were also present without associated fat. The macrophage accumulations and granulomatous changes were found not only in the intestinal mucosa and in the regional nodes but also in lymphatics leading from the bowel to the nodes, upon the peritoneal surfaces, along the lacteals, and in distant lymph nodes.

Changes in peripheral lymph nodes are of special value in establishing the diagnosis without laparotomy. The diagnostic significance of positive periodic acid-Schiff (PAS) macrophages in an axillary lymph node has been discussed in another paper [*15*]. Peripheral nodes were examined in three other patients. Axillary

nodes in two patients contained PAS positive macrophages, but an epitrochlear node in the third patient showed nothing of significance.

In addition, foam cells were observed in the hepatic portal triads in association with lymphocytes, in the heart valves, in the appendix and in the mucosa of the colon. It is of special importance that PAS stains be made in order to find the foamy macrophages because they are very easily overlooked in hematoxylin and eosin stained material.

In three of the five cases at autopsy there was bacterial endocarditis due to gram-positive cocci, identified as Streptococcus viridans in one instance. The aortic, tricuspid and mitral valves were involved. In one case there was a severe pericarditis as well, and both the mitral and tricuspid valves were thickened. A small myocardial infarction was found in one patient.

In two cases widespread pleural adhesions were found, associated with an extensive lobular pneumonia and embolic infarctions. In two cases the liver was large and pale, and microscopic examination revealed an inflammatory infiltration composed of lymphocytes and foam cells in the portal triads, and fatty changes were noted in three cases. The spleen was enlarged in two cases.

The striking histochemical feature of the characteristic macrophages in Whipple's disease is the presence of PAS positive particles [*19*]. The PAS positive material usually occurs in the form of small, rod-shaped masses, described as "sickle-formed particles" by Sieracki [*20*], which are located particularly in the perinuclear areas, which suggests their identification with mitochondria. Most of the PAS positive masses were larger and more round, and seemed to be located around small cytoplasmic vacuoles or distorted, ballooned mitochondria.

The PAS reaction of the macrophages of the intestine differed from that of the goblet cells of the mucosal epithelium in being a darker red. The alcian blue reaction of the macrophages varied from the presence of a few positive granules in some cells to a diffuse blue-staining of other cells. Nearly all macrophages that were PAS positive were alcian blue positive. However, many macrophages that were intensely stained with PAS were only faintly stained with alcian blue. This variable alcian blue reaction of the PAS positive macrophages indicates that acid mucopolysaccharides can not be the only material responsible for the PAS reaction. A variable amount of fat, stained with sudan red, was found within some PAS negative macrophages, and fat was especially prominent within the large spaces of the mesenteric lymph nodes. However, some mesenteric nodes were found to contain no large spaces and no fat. Iron was frequently found within the macrophages, particularly in the lymph nodes. With the Fontana silver technic for argentaffin granules, the mucicarmine stain for mucin, and the sudan black stain for formalin-fixed fat or phospholipid, a faintly staining macrophage or one containing a few granules was noted occasionally, but these reactions were usually negative. Special studies for glycogen of all of the tissues in one case revealed no significant deposits.

CLINICAL COURSE

The clinical courses in Cases I, II, III and IV, which have been presented in detail by Hendrix et al. [*14*], were steadily downhill, with progressive weight loss, continuing diarrhea, and death twelve to fourteen months after the onset of symptoms. None of these patients received antibiotics or adrenal steroids except one (Case IV), who was given adrenal cortical extract for four days prior to death.

One patient (Case V) was first hospitalized three months after the onset of symptoms. He was given blood transfusions, vitamins (including folic acid orally), and liver extract. His diarrhea did not improve, but he gained some weight. He again became anemic, and was readmitted for exploratory laparotomy, which confirmed the preoperative diagnosis of Whipple's disease. He was given 300,000 units of penicillin daily for five days postoperatively. His appetite improved, and diarrhea did not recur for several weeks. With the return of diarrhea, however, further weight loss and a decline in serum albumin and in hemoglobin values ensued, the latter falling from 11.6 to 8.7 gm. per 100 ml. in fifteen days. During his last admission, adrenal cortical extract was first given intramuscularly and then cortisone intramuscularly, 100 mg. daily, the latter for fourteen days, with slight weight gain but no symptomatic improvement. He continued to lose weight and died at home fifteen months after the onset of the abdominal symptoms.

One patient (Case VI) died of a massive pulmonary embolus on the eleventh day after the

exploratory laparotomy by which the diagnosis was made. There is little information as to the course of his illness prior to surgery.

In Case VII a history of symptoms of long duration and slow progression was given. Arthralgia and weight loss began in 1944. Episodic diarrhea, aching periumbilical pain and vomiting began in 1949. By 1952 anemia was severe enough that transfusions were given. By 1954 his weight had fallen from 180 to 115 pounds. The first prolonged episode of diarrhea, which was associated with marked anorexia, weakness and weight loss, persisted for four months and failed to respond to symptomatic therapy. However, the diarrhea ceased within twenty-four hours after beginning a course of chlortetracycline. Subsequent recurrences of diarrhea responded repeatedly to as few as six or eight capsules of chlortetracycline (total dose), and he gained weight, reaching 140 pounds at one point. However his general decline was not arrested. A preoperative diagnosis of Whipple's disease was confirmed by laparotomy in February, 1954. He was given procaine penicillin, 600,000 units daily, and streptomycin, 1 gm. daily, for eleven days postoperatively. Intravenous corticotropin was given concomitantly and was followed by oral cortisone, 100 mg. daily, which he continued for three months, and by stilbestrol, 2 mg. daily, which he took for eight months. A dramatic remission ensued, with disappearance of diarrhea; and, although the patient had a series of bone fractures which were attributable to severe osteoporosis and osteomalacia, he ultimately recovered and gained to 160 pounds. The hemoglobin, serum albumin and serum calcium values returned to normal. He has remained well. When last seen, in January, 1959, he had taken no medication and had been working daily. He declared that he had not "had a sick day" since leaving the hospital in 1954. He had had no recurrence of arthralgia, abdominal pain or diarrhea. His appetite was good, and he weighed 169 pounds.

In Case VIII the course had been steadily downhill for five months until a remission occurred after an exploratory laparotomy. Neomycin, 2 gm. every six hours, had been given for three days preoperatively, procaine penicillin, 600,000 units daily, and streptomycin, 1 gm. daily, were given for nine days postoperatively. He was maintained on a gluten-free diet, but he was given neither corticotropin nor steroids. During the ensuing remission, which lasted twelve months, he had neither diarrhea nor arthralgia and regained his normal weight of 145 pounds. Six months postoperatively he was re-evaluated and was found to have maintained his normal weight and to have normal vitamin A tolerance and triolein absorption. The plasma carotene was 178 μg. per 100 ml. The roentgenogram of the small bowel was improved but was not normal.

One year postoperatively the patient had a relapse, quite sudden in onset, with arthralgia, diarrhea, anorexia, and a loss of 18 pounds in ten days. He was readmitted for steroid therapy. He was afebrile, and the white blood cell count was normal. The stool guaiac test was strongly positive. Results of a triolein absorption test were abnormal, with a fecal value of 16 per cent of administered dose. There was little improvement on prednisone, 15 mg. four times a day, and a thrombosis of the left femoral artery and perforation of the sigmoid colon complicated his course. The patient survived an emergency laparotomy with closure of the sigmoid perforation on the thirty-ninth hospital day, and amputation of the left leg on the sixtieth day. Intramuscular tetracycline 200 mg. every six hours, had been started on the thirty-fifth day. This was later increased to 250 mg. orally every six hours and was continued for thirty-four days. Combiotic,® 2 ml. intramuscularly daily, was given for sixteen days after the last operative procedure. Seven months after closure of the sigmoid perforation the patient weighed 130 pounds despite loss of the leg. He was having no diarrhea, the hemoglobin was 15.8 gm. per 100 ml., and results of a triolein absorption test were essentially normal. When last contacted, in May 1960, seventy-six months after the onset of diarrhea, he was doing well, having no pain or diarrhea, weighing 154 pounds and working every day on his farm.

In Case IX the mildest manifestations were exhibited of any of the cases reviewed. The patient lost only twenty pounds before experiencing a lasting remission. Neomycin and Kaopectate® had been given at the onset of diarrhea, with considerable benefit, and diarrhea had been absent for nine months upon admission, his complaint being abdominal pain, rigors and weight loss. Surgery was performed, and a diagnosis of Whipple's disease was made. Postoperatively, tetracycline was given orally, 1 gm. daily for six days, and he was essentially symptom free at discharge. One month later pain and

fever recurred, and antibiotics and x-ray therapy totaling 1,000 roentgens to the abdomen were administered. A remission followed, and he has remained well and has worked every day since. He has not been given steroids or corticotropin at any time. He was re-evaluated in March 1958, at which time he was asymptomatic, weight 160 pounds, blood pressure 120/70 mm. Hg, no lymphadenopathy, abdomen noncontributory, hemoglobin 13.6 gm. per 100 ml. and the erythrocyte sedimentation rate 11 mm. per thirty minutes (Cutler, normal: 10 mm. per thirty minutes). When last contacted in October 1959, he stated that he was feeling entirely well and that he weighed 165 pounds.*

One patient (Case x) has been presented in detail elsewhere [*15*]. This man showed slight improvement during intravenous corticotropin therapy, but after returning home on a regimen of cortisone orally, 75 mg. daily, he declined rapidly and died five months after the onset of diarrhea. He was given no antibiotics.

A second patient (Case xi) has been reported on in detail elsewhere [*16*]. For seven months he had noted weakness, malaise and anorexia. There was progressive weight loss and low grade fever. Exploratory laparotomy elsewhere revealed a large mass of mesenteric lymph nodes, biopsy of which revealed "granulomatous inflammation, suggestive of histoplasmosis." Postoperatively, a spiking fever to 105°F. developed, which continued until admission, being unaffected by antibiotics or x-ray therapy. Thirteen years previously he had a bout of acute arthritis and subsequently had intermittent arthralgia. Peroral intestinal biopsy revealed changes characteristic of Whipple's disease.

He was given ACTH, penicillin and streptomycin. On this regimen he became afebrile, and two months after institution of therapy he had gained thirty-five pounds. He has remained well up to the present, one year after institution of therapy, during which time he has received dexamethasone daily orally. Roentgenograms of the small intestine in May 1960 revealed no abnormalities, and results of his absorption studies had likewise returned to normal. Intestinal biopsy in January 1960, showed improvement, and in May 1960, many villi were entirely normal.

A third patient (Case xii) likewise has been reported on in detail elsewhere [*17*]. She complained of diarrhea of six months' duration. Seven years prior to admission arthritis involving both ankles and hips, the fingers of both hands and the sternomanubrial joint developed. There was no fever, pigmentary change or hives. She had lost 42 pounds (from 110 to 68) during her illness. Tissue obtained by per oral intestinal tube biopsy revealed changes characteristic of Whipple's disease. She was given penicillin, tetracycline and ACTH daily for two weeks. This was accompanied by improvement in her sense of well-being, a weight gain of 15 pounds, and cessation of her diarrhea. Upon discharge she was given dexamethasone, 0.75 mg. four times a day. One month later she had gained an additional 8 pounds and felt entirely well. When last seen on May 2, 1960, six months after institution of therapy, she was still well, had gained a total of 30 pounds, and results of her absorption studies had returned entirely to normal.

* We are indebted to Dr. Henry Fuller, Watson Clinic, Lakeland, Florida, for the follow-up information on this patient.

COMMENTS

In 1907, George Whipple first described the disease which now bears his name. At that time and for many years, there have been a number of misconceptions concerning this disease. The term intestinal lipodystrophy, which is commonly used, suggests that the disorder involves the small intestine and is a disturbance of fat metabolism. Although the small intestine is involved primarily, there is now good evidence that this is also a systemic affection involving all tissues of the body. Although Whipple himself recognized that the material in the macrophages would not stain for fat, it was not until 1949 that Black-Schaffer [*19*] demonstrated that the material was a glycoprotein or a mucopolysaccharide.

At one time the disease was thought to be rare and invariably fatal, being diagnosed only by laparotomy or at autopsy. Our experience and a review of the recent literature indicate that the disease is not as rare as was formerly thought, that the diagnosis should be suspected clinically and confirmed without laparotomy, and that recovery may follow proper therapy.

The disease should be suspected in any patient with arthralgia, diarrhea, abdominal pain and weight loss. However, it is of interest that in our series of twelve patients, three had no diarrhea at any time, and one presented a problem in fever of unexplained origin. Lymphadenopathy and pigmentation, present in only half of our patients, were the most important physical

findings. Anemia was usually observed, and evidence of impaired absorption was the rule. In our patients, roentgenogram of the small bowel, when made, invariably showed abnormalities.

The diagnosis should be suspected on clinical grounds, although tissue confirmation is essential. In the past, biopsy of a mesenteric lymph node has been employed most often. Occasionally, laparotomy can be avoided by biopsy of a peripheral lymph node if the characteristic lesions are found [*9,15*]. Three axillary lymph nodes biopsies revealed characteristic PAS positive foam cells, whereas one epitrochlear node was negative. Biopsy of the small intestinal mucosa by means of the peroral biopsy tube [*21*] is the procedure of choice and established the diagnosis in two of our cases [*16,17*]. Three other patients, so diagnosed, have been reported [*22–24*].

The etiology of the disease is unknown. The demonstration of elevated anti-streptolysin O titers of the blood by Clemmesen [*25*] and by others [*8,10*] in a few cases has suggested the possibility that this disorder may represent a manifestation of the body's response to a beta-hemolytic streptococal infection. The cause of the abnormal accumulations of mucopolysaccharide and the mechanism of the disordered fat absorption and mobilization are as yet unexplained, and although some evidence has been presented that lymphatic obstruction may be responsible for the latter [*26*], there are strong arguments against this [*14*].

It is of interest to review the twelve patients who have responded to therapy [*2–13*] and to speculate upon the most likely cause of their recovery. Some observers [*2,8*] have reported striking remissions following antibiotic therapy. Others [*3–5,10–12*] have attributed recovery to ACTH or adrenocortical hormones. In most if not all of the patients in the latter group, antibiotics were used at the time of operation and it may be that both of these therapeutic agents played a role. Our experience would lend support to the belief that both forms of therapy should be employed. Two of the five patients of our series who are alive and well (Cases XI and XII), were given ACTH and antibiotics simultaneously with dramatic recovery. In Case VII antibiotics were given with temporary improvement only. Following the simultaneous administration of ACTH and antibiotics, he experienced a striking remission and has remained well during the past six years. The fourth patient had a complete remission on a gluten-free diet and antibiotics. He relapsed one year later and then was given steroids along with antibiotics and has remained symptom-free for the past six years. The fifth patient whose symptoms were the mildest of the entire group received antibiotics only. This patient has remained well for the past five years.

Of the remaining four who were diagnosed during life, one died during the postoperative period of a pulmonary embolus, one received ACTH and cortisone alone, one received ACTH four days before death, and the fourth received penicillin and cortisone only. Our observations and those of others would suggest that the treatment of choice is the combination of antibiotics and ACTH followed by adrenocortical steroids.

SUMMARY AND CONCLUSIONS

Twelve patients with Whipple's disease, the diagnosis confirmed by autopsy or biopsy, who have been seen in the past twenty-four years on one medical service are reviewed. Of the twelve, nine were diagnosed during life, and in six the diagnosis was suspected clinically before biopsy. Five of these patients were alive and well when last contacted, six to seventy-seven months after establishment of the diagnosis.

The following conclusions may be drawn: (1) The diagnosis of Whipple's disease can and should be made during life. (2) Biopsy of a peripheral lymph node or peroral biopsy of the intestinal mucosa may suffice to confirm the diagnosis. (3) Combined antibiotic and steroid therapy may induce a remission and is indicated. (4) The disease is not necessarily fatal.

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Pulmonary Function in Asbestosis of the Lung*

An Alveolar-Capillary Block Syndrome

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THE term "asbestos" is applied to several fibrous magnesium silicates which differ in their physical and chemical properties. About 95 per cent of commercially produced asbestos is chrysotile, 3 per cent crocidolite, and 2 per cent amosite [*1*]. Their high resistance to heat and acids, and their great tensile strength have led to widespread commercial use. Smith [*1*] quotes the world production in 1954 at 1,500,000 tons. It is not surprising, therefore, that respiratory involvement due to exposure to the particulate asbestos fibers during the manufacturing process should be an increasing problem.

Asbestos dust when inhaled produces lesions which differ sharply from the lesions of silicosis resulting from inhalation of silica (silicon dioxide). For the most part, the damage in asbestosis is a result of physical rather than chemical "irritation" [*2*] and results, pathologically, primarily in alveolar involvement of a diffuse nature.

The consequences of such involvement on pulmonary function have received attention in a number of studies. Roemeld, Kempf and Welder [*3*] described hyperventilation, decreased maximum breathing capacity and decreased oxygen saturation on exercise. Baldwin, Cournand and Richards [*4*] described a patient with impaired oxygenation of the blood. Gernez-Rieux, Balgaires and Clalys [*5*] found in three cases a reduced vital capacity, increased residual volume and a well preserved maximum breathing capacity. In asbestos workers with ten or more years of exposure, Gregoire [*6*] reported reduced arterial blood oxygen saturation in some cases. There was infrequent occurrence of emphysema (which so commonly accompanies silicosis). Wright reported well preserved maximum breathing capacity (except in very advanced cases), slight decrease in lung volume and an increase in A-a gradient suggestive of impaired diffusing capacity [*7*]. Bastenier et al. [*8*] in a thorough study of nine patients with prolonged exposure reported decreased vital capacity, well preserved maximum breathing capacity, hyperventilation and impaired arterial oxygen saturation. In all these studies the data relevant to arterial oxygen saturation suggested that there might be reduced diffusing capacity of the lung for oxygen. However, detailed studies of the diffusing capacity of the lung in asbestosis are not available.

The present report records the results of pulmonary function studies in seventeen workers exposed to asbestos dust for varying periods of time. In five cases the diffusing capacity of the lungs was measured.

MATERIALS AND METHODS

All seventeen patients included in this study had been employed in asbestos factories. They had varying degrees of clinical symptomatology and lung involvement on roentgenographic examination. (See Table 1.) All patients had been exposed to asbestos dust for years (range four to twenty-four years; average eleven and a half years).

In each case a detailed history was elicited with particular reference to occupational exposure to asbestos dust or other offending agents, which included not only the duration of exposure but also the intimacy of contact with the dust, the degree of exertion (increased ventilation) of the worker and the concentration of dust in the inspired air. Table 1 contains a summary of the exposure for all cases presented herein. They are graded from 1 plus to 4 plus as follows: 1 plus, constant or frequent exposure to

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TABLE I

CLINICAL FINDINGS IN SEVENTEEN PATIENTS WITH CHRONIC ASBESTOSIS

Case No.	Age (yr.)	Exposure		Roentgenographic Changes	Dyspnea	Cough	Signs and Symptoms of Bronchitis	Clubbing	Electrocardiogram	Asbestos Bodies	Abnormal VP and CT*
		Years	Intimacy								
1	48	14	3+	3+	2+	0	0	+++	0	0.1 mo.	0
2	43	12	4+	4+	3+	1+	±	+++	0	0.2 yr.	0
3	35	11	3+	3+	3+	2+	0	+++	0	0.15 mo.	0
4	66	10	3+	3+	0	0	0	0	0	+.2 yr.	0
5	42	13	2+	1+	2+	1+	+	+++	0	0.1 mo.	0
6	67	11	2+	2+	2+	2+	++	0	0	0.1 mo.	0
7	62	10	2+	1+	4+	3+	+++	++	0	+.2 mo.	0
8	46	24	4+	1+	1+	2+	0	+	0	0.3 mo.	0
10	36	13	3+	2+	0	3+	+	+	0	+.2 yr.	0
11	51	6	3+	2+	1+	1+	0	0	0	...	0
12	48	13	3+	2+	3+	2+	++	+++	0	+.1 mo.	0
13	63	13	1+	1+	0	0	0	0	0	0.1 mo.	0
14	67	11	4+	3+	0	0	0	0	0?	...	+
15	37	7	3+	0	1+	0	0	0	0	+.2 mo.	0
16	38	4	4+	0	0	2+	0	0	0	0.1 yr.	0
17	54	8	4+	3+	1+	2+	0	++	0	...	0
18	58	12	1+	0	0	0	0	0	0	+.2 w.	0

* VP indicates venous pressure; CT indicates circulation time (arm-to-tongue).

minimal asbestos dust concentrations, e.g., warehouse work or dusty work in open areas, or intermittent exposure in heavily contaminated areas, e.g., maintenance work; 2 plus, as in 1 plus but with greater concentration of dust in air, e.g., work on feeding machines; 3 plus, constant exposure to very high concentrations of asbestos dust, with heavy manual exertion required, e.g., sawing machine work or grinding; 4 plus, maximal exposure to highest concentrations of dust and intimate contact, e.g., workers in a room which is the terminus of the factory exhaust-dust collecting system.

Insofar as the use of a mask for protection is concerned, almost all workers complained that they were too uncomfortable to be worn constantly. This discomfort and frequency of omission of the mask increased with the physical requirements of the work and with the workers' sense of becoming overheated. Moreover, the masks varied in the efficiency of protection they afforded, particularly after protracted use. Even with use of a mask, it was the usual experience that the worker's nose and mouth were covered with asbestos dust at the end of a working day.

In Table I are listed some of the principal features of history and physical examination, graded from 1 plus (minimal) to 4 plus (severe). In addition to routine clinical laboratory tests, in fourteen of the seventeen cases sputum was examined at least once for asbestos bodies and all were cultured for tubercle bacilli. An electrocardiogram and anteroposterior and lateral roentgenograms of the chest were obtained in each case. Roentgenograms were graded from 1 plus to 4 plus based on the degree of pulmonary involvement. The factors were: (1) parenchymal infiltration, degree and extent; (2) diminution in vascular markings; and (3) diaphragmatic and pericardial adhesions. Of these features parenchymal infiltration was considered the most important factor.

The circulation time, arm-to-tongue (Decholin®), and venous pressure were also measured. Measurements of lung volumes, maximum breathing capacity, index of intrapulmonary mixing, ventilation, arterial oxygen saturation and carbon dioxide content were carried out according to the methods of Baldwin, Cournand and Richards [*9*]. The partial pressure of oxygen in the arterial blood was measured by the direct technic of Riley, Proemmel and Franke [*10*]. By use of two levels of inspired oxygen concentration the ventilation-perfusion relationships of the lung and the diffusing capacity of the lung for oxygen were calculated by the method of Riley and Cournand [*11,12*]. From this analysis the data for the physiological dead space, venous admixture and diffusing capacity of the lung were obtained.

RESULTS

The results are presented in Tables I, II, III and IV.

Lung Volumes. The *vital capacity* was fairly

TABLE II

Case No.	Vital Capacity		Residual Volume		Total Lung Capacity		Residual Volume / Total Lung Capacity (%)	Maximum Breathing Capacity		Index of Intrapulmonary Mixing (%)
	Observed (cc.)	% Predicted	Observed (cc.)	% Predicted	Observed (cc.)	% Predicted		Observed (L./min.)	% Predicted	
1	2,375	56	1,153	87	3,413	56	33.7	123	100	1.29
2	2,580	65	950	74	3,830	73	24.8	116	113	1.20
3	2,457	53	1,961	171	4,418	76	44.0	101	81	4.50
4	3,750	88	1,500	109	5,250	93	28.6	134	131	2.20
5	5,220	117	2,060	142	7,110	120	29.0	146	120	1.25
6	3,060	77	1,345	104	4,285	81	31.4	111	120	2.46
7	2,900	71	2,145	162	6,090	112	35.0	90	113	3.02
8	4,055	97	1,265	94	5,320	96	23.8	105	88	2.02
9	4,680	98	1,400	91	6,080	96	23.0	133	88	1.79
10	3,840	90	1,590	115	5,430	96	29.3	134	106	1.12
11	2,510	68	1,563	131	4,513	92	35.0	87	81	3.00
12	2,910	65	1,450	100	4,360	73	33.0	111	101	2.42
13	3,300	107	1,200	121	4,500	112	26.6	70	87	2.61
14	5,036	124	1,619	124	6,715	125	25.0	90	86	1.43
15	4,630	81	1,300	94	3,330	77	28.1	152	118	2.00
16	3,510	82	1,380	100	4,890	86	28.0	99	99	2.01
17	2,945	70	1,555	115	3,800	69	40.9	140	133	2.42

TABLE III

ALVEOLAR VENTILATION AND DEAD SPACE

Case No.	$\dot{V}O_2/M^2$ (cc./min.)	$\dot{V}_E$ (L./min./M²)		Ventilatory Equivalent (L./100 cc. O_2)	Arterial Blood O_2 Saturation (%)		Resting P_{CO_2} (mm. Hg)	Dead Space / Total Ventilation (%)
		Rest	Exercise		Rest	Exercise		
1	145	3.56	11.52	2.45	90	71	40	25
2	151	5.19	20.18	3.44	93	78	41	42
3	140	4.39	13.55	3.14	95	83	41	36
4	140	4.52	13.96	3.20	93	86	42	30
5	126	4.46	13.55	3.54	95	88	37	40
6	131	4.58	11.35	3.84	93	89	43	31
7	156	5.98	16.55	3.83	94	90	41	40
8	133	4.13	12.52	3.11	96	91	43	27
9	129	4.43	14.10	3.44	97	92	38	32
10	143	4.89	14.50	3.42	95	92	40	35
11	138	5.15	14.30	3.73	93	94	43	37
12	120	3.11	10.67	3.86	95	95	40	37
13	166	5.81	8.52	3.50	98	95	40	33
14	138	3.30	14.50	2.39	95	95	43	36
15	141	5.26	...	3.73	96	95	42	25
16	149	6.56	17.67	4.40	95	96	40	42
17	140	3.96	9.08	2.83	95	96	40	26

TABLE IV

VENTILATION PERFUSION RELATIONSHIPS AND OXYGEN DIFFUSING CAPACITY IN FIVE PATIENTS WITH PULMONARY ASBESTOSIS

Case No.	Alveolar p_{O_2} (mm. Hg)		Alveolar-Arterial O_2 Gradient (mm. Hg)		Diffusing* Capacity of Lung for O_2 (cc./min./mm.)	Venous† Admixture (%)	Dead Space / Total Ventilation (%)
	21% O_2	16% O_2	21% O_2	16% O_2			
1	102	70	22	25	9	10	25
6	106	70	26	14	10	12	31
7	100	67	16	13	9	8	40
3	105	73	14	7	14	6	30
4	104	68	29	14	15	16	30

* Diffusing capacity of the lung for oxygen expressed as cubic centimeters of oxygen per minute for mean millimeter pressure difference between mean alveolar oxygen tension and pulmonary capillary blood oxygen tension.

† Venous admixture expressed as per cent of cardiac output.

well preserved (80 to 100 per cent of the predicted value) in half the patients. In six patients it was 60 to 80 per cent of predicted, and in two patients (Cases 1 and 3) it was less than 60 per cent of predicted. It is of interest that one of these patients (Case 1) had a residual volume to total capacity ratio which was within normal limits, reflecting a uniform reduction in lung volumes.

The residual volume did not differ significantly from the predicted figures in ten cases. In six it was significantly increased to a figure 20 per cent or more greater than the predicted. Despite these findings the calculated residual volume to total capacity ratio was within normal limits in all but two patients (Cases 3 and 17).

The total capacity did not differ significantly from normal in eleven cases and was moderately reduced in six.

In general, vital capacity and total capacity were well preserved or only moderately decreased. The residual volume was well preserved or moderately increased, with abnormally high RV/TC ratios in only two cases.

Maximum Breathing Capacity. The maximum breathing capacity was well preserved in all patients, being greater than predicted in ten and within 80 to 99 per cent of predicted in the remaining seven cases. It is of interest that in two patients (Cases 3 and 17) the maximum breathing capacity was 81 and 133 per cent of predicted, respectively, in spite of the elevated RV/TC ratios.

Intrapulmonary Mixing of Gases. The index of intrapulmonary mixing was less than 2.5 per cent in all but three patients in whom it was 3, 3.02 and 4.50 per cent, respectively. The highest value (4.50 per cent) was obtained in Case 3 where the RV/TC ratio was 44 per cent.

Ventilation. At rest the minute ventilation exceeded 4 L./min./M^2 in thirteen of the cases. Of these, six were in excess of 5 L./min./M^2. In all but two cases it was greater than 3.5. On standard exercise, marked hyperventilation was present in three (greater than 15 L./min./M^2), and ventilation was greater than 10.6 L./min./M^2 in eleven additional instances, that is, three-fourths of the patients had hyperventilation on exercise. In one patient (Case 15) it was not measured.

Arterial Oxygen Saturation. The arterial oxygen saturation at rest was greater than 95 per cent in eleven cases. Of these, five became moderately unsaturated on exercise. The arterial oxygen saturation at rest was 94 per cent in one patient and 93 per cent in five, four of whom had a further decrease in saturation on exercise. All told, ten patients had arterial oxygen saturation values of 92 per cent or less on exercise, the lowest being 71 per cent.

Alveolar Ventilation and Dead Space. Total minute ventilation was usually increased. Alveolar ventilation was also increased but not, however, to the same extent, as indicated by the fact that dead space ventilation expressed as per cent of tidal volume was increased to or exceeded the upper limit of normal in twelve patients. (Table III.) In no case was alveolar ventilation significantly reduced.

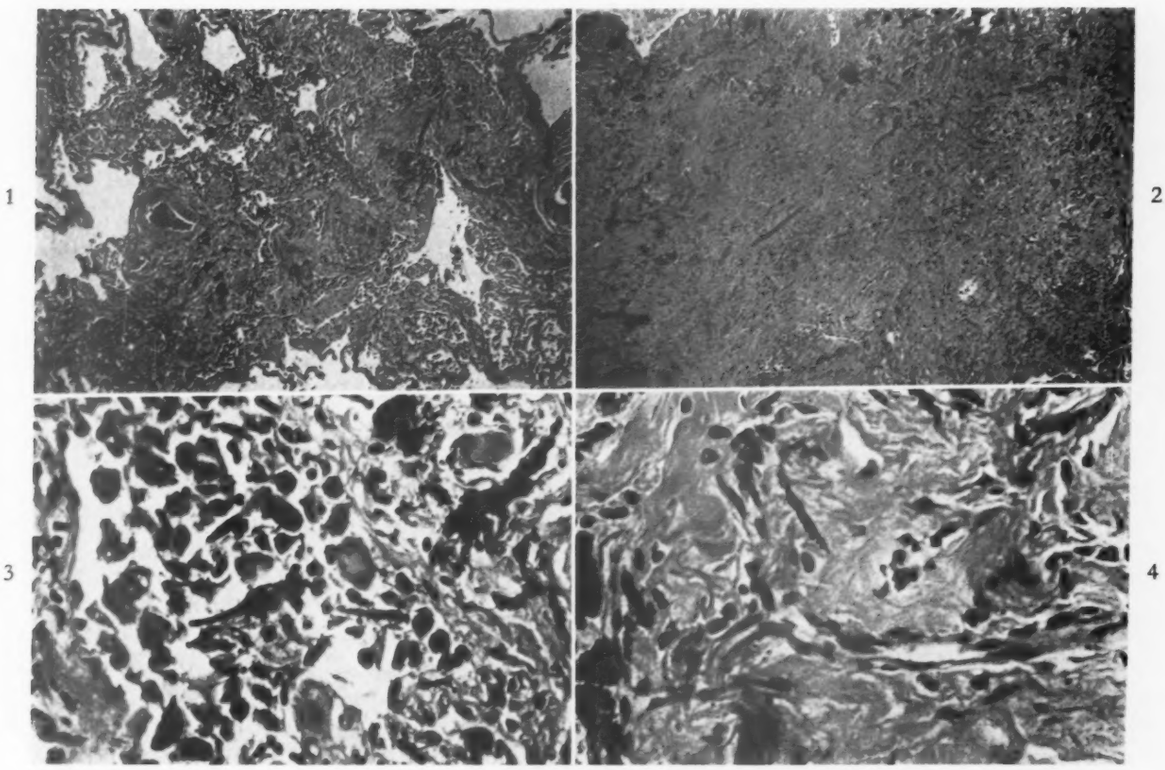


FIG. 1. Perivascular fibrosis and septal alveolar fibrosis, × 75.

FIG. 2. Diffuse fibrosis, × 75.

FIG. 3. Alveolar space filled with macrophages and asbestosis bodies, × 400.

FIG. 4. Asbestosis body in an area of fibrosis, × 400.

Diffusing Capacity. In an attempt to analyze the mechanism for the fall in oxygen saturation, an analysis of the A-a gradient at two levels was carried out according to the method of Riley and Cournand [*11*]. The results in five cases so studied are listed in Table IV. These data were collected at rest. The diffusing capacity was found to be less than 15 cc./mm./min. in four of the five cases, and the venous admixture was increased to greater than 6 per cent in all but one.

COMMENTS

Pathology. Prior to consideration of the physiologic alterations in these workers exposed to asbestos dust, it would be relevant to review some of the data on the production of the asbestos lesions in the lung. (Figs. 1, 2, 3 and 4.) Magnesium silicate fibers up to 50 μ to 100 μ or even more in length, when inhaled for several years, damage the walls where they lodge [*1*]. Vorwald, Durkan and Pratt [*2*] have shown this to be a physical reaction in contrast to the chemical reaction that occurs in silicosis. The fibers themselves are usually deposited in the terminal bronchioles where a tissue reaction ultimately covers them and leads to formation of "asbestos bodies." Such "bodies" may be found in patients with short exposure and their presence does not correlate with the degree, if any of pulmonary damage. The asbestos body itself consists of a fiber enveloped by foreign body giant cells, and is covered with a smooth coating apparently of colloidal nature. The asbestos fibers are too large to permit ready drainage into the lymphatic system; accordingly, few (and only the smaller fibers) are deposited in lymph nodes and fewer still reach mediastinal nodes [*13*]. As Lynch points out, this limited opportunity for invasion of the lymphatics explains another difference between silicosis and asbestosis. Silica particles, small in size, easily penetrate alveolar walls and deposit in the lymphatic system, causing focal reaction and characteristic nodular fibrosis. Asbestos particles, on the other hand, lodge particularly in the vestibular areas of the

lobules and in the alveoli, and elicit a more uniformly distributed, diffuse (non-nodular) fibrosis. Continued exposure leads ultimately to further damage, and scarring in the areas of deposition.

Lynch [*13*] has proposed four grades of involvement, which may briefly be summarized as follows: grade I indicates incidental finding of asbestos bodies without clinical disease or apparent abnormality. Grade II (also an incidental finding) indicates that asbestos bodies are seen in alveoli and scattered through the fibrous tissue of the lung. There is also thickening of the alveolar walls and some perivascular fibrosis. Grossly there is little found other than some coarseness of the parenchyma. Grade III indicates that the lung is coarsely honeycombed, fibrous in texture, non-elastic and distended. The process is generally uniform and there are patches of scar tissue; pleural thickening occurs also. Grade IV is associated with advanced cardiorespiratory failure. The lungs are coarse, inelastic, fixed in expansion, and greyish-marbled on cut section. There is extensive fibrous induration, with scars in patchy distribution. Pleural thickening may progress to a brittle firmness.

Physiology. In the cases studied there was little abnormality in lung volume, except for occasional moderate reduction in vital capacity without significant increase in residual volume. Maximum breathing capacity was well preserved.

Hyperventilation was present at rest and particularly on exercise. Arterial hypoxemia was observed in some cases at rest, but more frequently on exercise. In contrast, there were normal, or only slightly reduced arterial P_{CO_2} tensions and normal distribution of inspired gas.

Physiological dead space was normal or only slightly increased. Venous admixture was increased and the diffusing capacity of the lung for oxygen, as measured at rest, was reduced. These findings are characteristic of the syndrome of alveolar-capillary block as described by Austrian et al. [*14*].

Previous investigations of pulmonary function in asbestosis have noted some of the following findings: Roemeld [*3*] reported hyperventilation and reduction in arterial oxygen saturation on exercise, but his finding of a reduced maximum breathing capacity is not consistent with other reports; this suggests that he may have been dealing with advanced lung involvement, possibly with associated emphysema. A well preserved maximum breathing capacity was found by Wright [*7*], Gernez-Rieux et al. [*5*], and in the present study. Bastenier et al. [*8*] reported on nine patients with markedly prolonged exposure to a high concentration of asbestos dust (1,000 to 2,000 particles per cu. cm.) and the maximum breathing capacity was decreased in eight of nine cases. Indeed, these same authors report impairment of distribution of inspired gas in eight cases, and an elevated RV/TC ratio in seven cases, suggesting that extensive emphysematous involvement was present in their group, as is seen in advanced pneumonoconioses. It is noteworthy that five of these patients were recorded as having chronic bronchitis, suggesting the possibility that the emphysematous changes in these instances may not have been related to the asbestosis.

These findings contrast with our observation that signs and symptoms of bronchitis were present in only five of our seventeen cases, and in only one were these of any significance. In the largest series to date (fifty-seven patients), reported on by Wright [*7*], apart from the previously mentioned well maintained maximum breathing capacity there was only slight decrease in total lung volume, normal arterial carbon dioxide tension, and an increased A-a gradient due to a reduction in the arterial oxygen tension. These findings are not consistent with an emphysema-like pattern. Wright did, however, note that with extreme fibrotic involvement some reduction in maximum breathing capacity might take place. In Gregoire's study [*6*] no emphysematous changes were found to explain the reduced arterial oxygen saturation.

That alveolar-respiratory insufficiency, that is, impaired diffusion, was the probable cause of the hypoxemia has been suggested by others [*4,7*]. No previous study of the diffusing capacity of the lung for oxygen in workers suffering from asbestosis is available, however, except for a single case reported by Marks et al. [*15*]; on this patient (Case 9 in their series, noted as ? asbestosis), it was noted that there was a decreased diffusing capacity for oxygen and carbon monoxide and a slight increase in venous admixture. This patient had a slight decrease in maximum breathing capacity, normal RV/TC ratio, normal index of intrapulmonary mixing, and normal timed vital capacity. The standard vital capacity was slightly decreased. There was, furthermore, slight

hyperventilation at rest, and an oxygen saturation of 94 per cent at rest (no data on exercise).

The present study offers evidence that the physiologic abnormalities found in early and moderately advanced cases are primarily due to alveolar-capillary block. Only two of our patients (Cases 3 and 17) had elevation of the RV/TC ratio but in one (Case 17) the maximum breathing capacity exceeded the predicted figure and there was no increase in the index of intrapulmonary mixing; in the other, (Case 3) the maximum breathing capacity was 80 per cent of predicted but there was an increased index of intrapulmonary mixing, suggesting some impairment in the distribution of inspired gas. (See Table II.)

In the present series, those patients with physiologic abnormality had no evidence of significant airway obstruction and showed no evidence of emphysematous change in lung volume (with rare exceptions). The well maintained maximum breathing capacity, normal or low arterial carbon dioxide tension, hyperventilation at rest but more particularly on exercise, and a measured reduction in diffusing capacity all indicate the presence of an alveolar-capillary block syndrome.

The mechanisms proposed to account for dyspnea in this syndrome include early activation of Hering-Breuer reflexes, and associated increased sensitivity of the respiratory center due to hyperventilation with blowing off of carbon dioxide [*3*]. In general, pathologic alterations producing increased fibrotic reactions in the lung have been shown to result in an increase in the oxygen cost of breathing [*16*]. This increase in work of breathing possibly contributes to the production of dyspnea in pulmonary asbestosis, a view supported not only by the physiologic findings indicating the presence of an alveolar-capillary block but also by the pathologic changes already summarized.

Correlation of Physiological Findings with Duration and Intimacy of Exposure. It would be expected that increased duration and intimacy of exposure would lead to a higher concentration of the particulate asbestos fibers in the lung and greater opportunity for continued damage. Not all of our seventeen patients had demonstrable abnormalities of pulmonary function. The most common abnormality was a reduction in arterial oxygen saturation on exercise. Using this criterion, there is no correlation between the degree of functional impairment and the number of years of exposure to asbestos dust. (Tables I and III.) This is true also for intimacy of exposure (as defined in the methods section).

Correlation with Roentgenographic Findings. In general, there is a gross correlation of physiologic abnormalities and roentgenographic findings. (Tables I and III.) In two patients, however (Cases 14 and 17), there was marked (3 plus) involvement by roentgenograms without significant abnormality of lung function. More striking, however, was the finding of significant impairment of lung function with only minimal (1 plus or 2 plus) roentgenographic involvement (Cases 5, 6, 7, 8, 9 and 10). In all patients with functional impairment there was roentgenographic findings, and the four patients with the most functional involvement had 3 plus to 4 plus roentgenographic findings.

It has been established that there is no uniformity in the degree of involvement in persons with the same exposure [*7,13*]. It is also known that progress of the disease may be halted upon removal from exposure but the pathological changes already present are not reversible and continue their evolution [*13*]. Of interest in this regard (i. e., exposure and time duration after withdrawal from exposure) is the study of Knox and Beattie [*17*] who incinerated the lungs in twenty-seven cases of asbestosis and measured the mineral content of the ash. There was a variable increase in the amount of ash with increasing duration of exposure and a variable decrease on cessation of exposure [*17*]. The importance of the time factor in evolution of the disease is illustrated by the fact that the severity of the lesions these authors observed is related to the sum of the exposure and survival times and not to the mineral content of the lungs. Further support for this view is expressed by Lanza et al. who found that the percentage of positive cases (by roentgenograms) increased with duration of exposure: 43 per cent positive under five years exposure; 50 per cent at 5 and 10 years; 58 per cent in 10 to 15 years; 87 per cent over 15 years [*18*]. It may be concluded that while the percentage of positive cases of pulmonary asbestosis (proved by roentgenographic evidence) does appear to correlate with the duration of exposure, the physiologic findings in general do not, except that patients with marked roentgenographic evidence of pulmonary asbestosis usually have more significant reduction in pulmonary function.

SUMMARY

Seventeen workers exposed to asbestos dust were studied clinically and by pulmonary function tests. Vital capacity was well preserved in half of the patients and moderately reduced in the remainder. Residual volume was not significantly altered except for a slight increase in six patients. The RV/TC ratio was normal in all but two patients. Maximum breathing capacity was well preserved in all cases.

Analysis of ventilation-perfusion relationships revealed normal intrapulmonary mixing of gases in all but three subjects, in whom it was reduced. Hyperventilation was present at rest and exercise in the majority of patients. Arterial oxygen saturation was slightly reduced in six patients at rest, and lower than 92 per cent on exercise in ten patients. While dead space ventilation (expressed as per cent of tidal volume) exceeded the upper limit in twelve patients, alveolar ventilation was increased in absolute terms and in no case was it decreased.

The diffusing capacity of the lung for oxygen was measured in five patients at rest. In four of these it was reduced. In addition, in four of these five subjects venous admixture was increased.

These abnormalities in pulmonary function correlated poorly with intimacy and duration of exposure. A better correlation was found when compared with roentgenographic abnormalities.

The physiologic findings noted are characteristic of the alveolar-capillary block syndrome. The pathologic changes produced in asbestosis of the lung are reviewed in relation to this physiological syndrome.

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Reviews

The Veterans Administration-Army Cooperative Study of Pulmonary Function*

I. Clinical Spirometry in Normal Men

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OVER 110 years ago John Hutchinson [*1*] devised the spirometer and described and defined the vital capacity. Hutchinson's series of vital capacity measurements in over 2,000 healthy males (in addition to measurements in twenty-six "girls" and 360 "diseased cases") is still the largest reported. He pointed out that the vital capacity was directly related to height and inversely proportional to age in the thirty to sixty-five year age range. His classic analysis of the relation of height and weight to vital capacity concludes with the statement " . . . the weight can never be the sure guide that the height is, because the former varies at any time in life even in a few days; whereas the latter varies only at the extremes of life."

The simplicity and rapidity with which vital capacity could be measured led to an abundance of subsequent reports with tables of normal standards and formulas for prediction. Peabody and Wentworth [*2*] in 1917 related the vital capacity to body surface area, and Lundsgaard and Van Slyke [*3*] related this measurement to the calculated thoracic volume. Dreyer [*4*] in 1919 disagreed with Hutchinson on almost every point and related vital capacity to body weight, body surface area, stem length and chest circumference (based upon measurements made in only sixteen boys and men). West [*5*] related the vital capacity to both body surface area and to height and prepared quite simple prediction formulas from these relationships. These were modified slightly by Hewlitt and Jackson [*6*]. Myers [*7*] related the vital capacity to body weight, body surface area and to sitting height and established tables of normal standards based upon these relationships. Other reports have related vital capacity to chest expansion [*8*] and to age [*9,10*].

The modern period in pulmonary function testing would seem to date from the work of Cournand and Richards [*11*] first reported in 1941, later developing into the classic report of Baldwin, Cournand and Richards [*12*] which has served as a handbook for workers in the field for a number of years. Although Hermannsen [*13*] introduced the maximum breathing capacity measurement in 1933, the test did not gain widespread use until Cournand and his associates [*11,12*] evaluated this test and introduced regression equations for prediction of normal values.

In 1948 Tiffeneau and Pinelli [*14*] and later Gaensler [*15*] demonstrated the usefulness of the time-volume relation in the performance of the vital capacity. More recently attention has been called to the maximal inspiratory and expiratory flow rates [*16–18*] and the maximal mid-expiratory flow [*19*].

Despite the large number of reports in the literature, the normal standard tables and prediction formulas now available are not entirely adequate. In most instances the standard errors of such equations are large and an inadequate number, age range, or type of normal subject has been used for deriving the formulas. As

* The investigators and pulmonary function laboratories of the fifteen hospitals contributing to this study are listed under Acknowledgments.

pulmonary function testing has become increasingly important in the diagnosis and management of pulmonary disease, the need for standardization of technics and instrumentation has become apparent. In a recent review Gaensler [*20*] states: "A great need exists for the uninspiring task of obtaining statistically significant normal values for clinical ventilatory tests."

The standardization of procedures and the accumulation of data for establishing normal values cannot be accomplished easily in a single laboratory. The unique advantage of a cooperative study is the opportunity it affords for interchange of ideas and the analysis of data from a group of investigators. This permits detection of small but significant errors of technics and provides refinements acceptable to the participating laboratories. The medical facilities of the Army and the Veterans Administration are particularly suitable for a cooperative study of this type.

A planning committee for a cooperative study of pulmonary function testing was established in 1953, followed by a pilot testing program, standardization of spirometric methods, and the collection of data in normal males. A description of these methods and the analysis of the data from these normal subjects form the basis for this report.

SUBJECTS

Male subjects were selected from hospital employees, patients, medical students, resident and full-time physicians of the participating hospitals. Cardiopulmonary laboratory personnel were excluded because of their familiarity with the tests. The following criteria were required for acceptance as a subject: (1) no history of chronic cardiopulmonary disease or acute cardiopulmonary disease during the six-month period preceding the testing; (2) no evidenec from physical examination, chest roentgenogram and electrocardiogram of cardiopulmonary disease; (3) physically and mentally capable of adequate cooperation during the tests; (4) no manifest weakness or debility which significantly limits activity; and (5) no evidence or history of disease which can be expected to affect pulmonary function (such as neuromuscular disorders or arthritis of the spine).

For each subject height and weight were measured and the body surface area calculated [*21*]. The chest circumference and anteroposterior diameter (fourth costochondral junction) were measured in maximal inspiration and maximal expiration.

DESCRIPTION OF SPIROMETER SYSTEM

All spirometric measurements were made on Collins 13.5 L. recording spirometers with motor speeds of ⅛ r.p.m. and 4 r.p.m., the latter motor having been substituted for the 1/15 r.p.m. motor which is supplied with the instrument. The 4 r.p.m. motor is necessary in order to provide a paper speed sufficiently rapid (32 mm./second) to permit accurate measurements of the rapid expiratory tracing. Forced vital capacities were recorded with the 32 mm./second chart speed, but for all other testing the 32 mm./12 second chart speed was employed. For recording the forced expiratory spirograms with the 32 mm./second chart speed, it was necessary to prevent slowing of the kymograph drum resulting from the backward pull of the roll of paper. This was accomplished either by inverting the paper roll so that the non-printed side presented as the recording surface or by cutting sheets of recording paper and applying them individually to the kymograph drum. Whether plain or printed paper was used, vertical lines were inscribed on the paper by moving the bell up and down while the kymograph drum was stationary so that true vertical orientation of the tracing could be made. This also effectively rinses the spirometer system. The vertical lines permit detection and correction of any angulation in the application of the recording paper. The water level was maintained 4 cm. below the top of the spirometer tank. The level of the spirometer was routinely checked so that the bell maintained a vertical and free position even when it was high in the water. The bell was positioned so that the pen recorded in the mid-portion of the paper.

The 13.5 L. spirometer has 1.5 inch tubing and a ventilograph attachment. The CO_2 absorbing canister and valves were removed. The patient breathed through a rubber mouthpiece, and a noseclip was applied to prevent nasal breathing during the studies.

NOMENCLATURE

For this study the system of nomenclature proposed by Gandevia and Hugh-Jones [*22*] has been adopted as an extension of the nomenclature recommended by the Pappenheimer [*23*] committee. These terms and their symbols are outlined in Table 1.

SPIROMETRY TESTING PROCEDURE

The purpose of the test was explained to each subject and the methods of testing were demonstrated. The need for avoiding leaks around the noseclip and mouthpiece was emphasized. All questions by the subject were answered, and every effort was made to allay apprehension and promote cooperation.

All tests were performed with the subject in the standing position. Before each test the noseclip was applied and the patient instructed to blow or sniff through his nose with his mouth closed to test for leaks.

The precise technics used in the performance of the various tests are detailed as follows:

Vital Capacity (*VC*). The mouthpiece is placed in

TABLE I

TERMS USED FOR SPIROMETRIC MEASUREMENTS

Modified from Gandevia and Hugh-Jones [*22*]

Description	Term Used	Symbol	Other Previously Used Terms
A. Terms Which Apply to Single Breath Spirograms			
The maximal volume measured on expiration after the deepest inspiration	Vital capacity	VC	
The maximal volume measured on inspiration after a full expiration	Inspiratory vital capacity	IVC	
Volume of gas expired after full inspiration; expiration being as rapid and complete as possible (i.e., forced)	Forced vital capacity	FVC	Timed vital capacity; fast vital capacity; fast maximum expiratory capacity
Volume of gas exhaled over a given time interval during a complete forced expiration	Forced expiratory volume, qualified by time interval used in seconds	FEV_T	Timed vital capacity; fast expiratory capacity; forced expiratory volume; maximum expiratory volume
FEV_T expressed as percentage of the forced vital capacity	Percentage expired (in T sec.)	FEV_T %	Timed vital capacity; timed expiratory capacity
Spirographic tracing of a forced complete expiration	Forced expiratory spirogram	FES	Expirogram; fast expiratory vital spirogram
The volume of air exhaled per unit of time measured between the 200 ml. and 1,200 ml. volumes of the forced expiratory spirogram	Maximal expiratory flow rate	MEFR	
The volume of air per unit of time exhaled during the middle half of the *expired volume* of the forced expiratory spirogram	Maximal mid-expiratory flow	MMF	
B. Terms Which Apply to the Maximal Breathing Capacity (MBC)			
Maximal volume of air which a subject can breathe per minute	Maximal breathing capacity*	MBC	Maximum breathing capacity
Volume of air which a subject can breathe with voluntary maximal ventilatory effort for a given time (the direct measurement is made during 12 seconds, but the value is expressed in liters per minute)	Maximal voluntary ventilation	MVV_F	Maximum breathing capacity; maximum ventilatory capacity

NOTE: When inspiratory measurements are made, terms such as forced inspiratory volume (FIV_T) or forced inspiratory spirogram (FIS) may be used.

* Since the maximal breathing capacity may be assessed in several ways and under varying conditions (exercise, CO_2 inhalation and voluntary effort), the term MBC should be reserved to indicate a maximal value for a subject. The maximal voluntary ventilation (MVV) in liters per minute is the maximal volume of gas which the subject moves per unit of time when breathing as deeply and as quickly as possible, or when breathing as deeply as possible at a controlled frequency. When frequency is not controlled, the term used is maximal voluntary ventilation, free (MVV_F), but the frequency adopted by the subject should *also* be noted (thus, MVV_{F40}, MVV_{F60}). When the frequency is controlled, the F subscript is omitted, but the frequency actually used is indicated by a subscript as before (thus, MVV_{40}, MVV_{60}).

the patient's mouth and the kymograph operated at the slow speed (32 mm./12 second). After a baseline tracing of quiet breathing is obtained, the subject is instructed to inspire until the maximal inspiratory position has been recorded. The subject is then told to exhale smoothly and completely without force or haste until expiration is complete and then to continue with normal breathing. The vital capacity measurement is repeated until duplicate values are obtained which agree within 5 per cent.

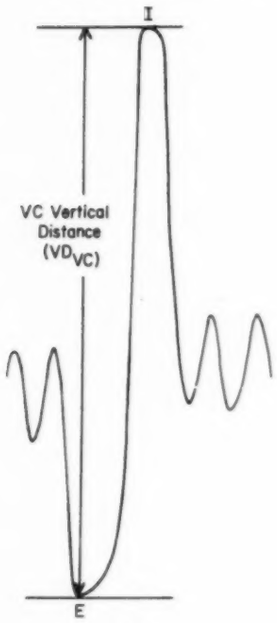


FIG. 1. Spirographic tracings: (a) vital capacity (VC), and (b) inspiratory vital capacity (IVC). Records are read from right to left. In (a) after a few quiet (tidal) breaths, a maximal inspiration is recorded, followed by maximal expiration. In (b) a maximal expiration is recorded first, followed by maximal inspiration. I = level of maximal inspiration. E = level of maximal expiration.

Inspiratory Vital Capacity (IVC). Upon completion of the VC (expiratory) determination, the mouthpiece and noseclip are removed and the spirometer rinsed again inscribing vertical lines for proper orientation of the paper. After a rest period of at least two minutes, the noseclip is reapplied, the mouthpiece reinserted, and a baseline of quiet breathing obtained. During normal expiration, the subject is instructed to continue exhaling smoothly and completely until maximal expiration has been recorded. When this point has been reached, the subject is instructed to inhale as deeply as possible and then to continue with normal breathing. Repeated efforts are made until satisfactory duplicate values are obtained.

Forced Vital Capacity (FVC). Again the mouthpiece and noseclip are removed and the spirometer rinsed. The subject is instructed and allowed to practice a forced rapid expiration from a position of complete inspiration. He is then connected to the spirometer and a baseline of quiet breathing recorded. The subject is told to inspire until the position of maximal inspiration is reached. At this time the kymograph, which has been recording at the slow speed (32 mm./12 second), is switched to the fast speed (32 mm./second), and the subject instructed to exhale as rapidly and completely as possible.

Maximal Voluntary Ventilation, Free (MVV_F). After the vital capacity efforts are completed, the subject is allowed to rest for at least five minutes. Instruction and a demonstration are given by the examiner. A noseclip is applied and the subject is connected to the spirometer. After a few tidal breaths are recorded with the kymograph at the 32 mm./12 second speed, the subject is told to breathe as deeply and rapidly as possible and is exhorted by the operator to accomplish this.

This procedure is continued until at least twelve seconds of such breathing have been recorded. Three such twelve-second periods of maximal ventilatory effort are recorded with at least five minutes rest between the trials.

The temperature of the spirometer is then recorded and is written on the record along with the date, the patient's name, height, weight, and age, and the technician's initials. The tracings are now ready to be measured and calculated.

MEASUREMENT OF SPIROGRAPHIC RECORDS AND CALCULATION OF VOLUMES AND FLOW RATES

Figures 1 through 6 are diagrams of spirographic tracings which illustrate the technics of the various measurements. These read from *right to left* because of the direction of rotation of the Collins spirometers used in this study. It is recognized that spirographic tracings which read from *left to right* are desirable, if the instruments could be modified appropriately.

The duplicate tracing exhibiting the larger volume for the various spirographic records was chosen for measurement. All the volume calculations are based on the vertical excursions of the recording pens. For each measurement the vertical distance between the two appropriate points expressed in millimeters is arbitrarily designated VD for this report.

The VD for each measurement is multiplied by a

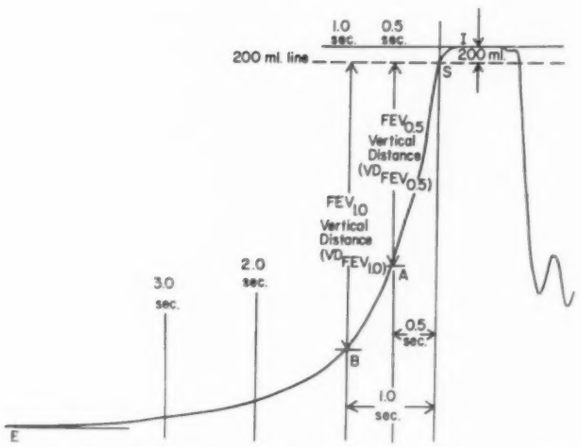


FIG. 2. Forced expiratory spirogram, illustrating measurement of the 0.5 and 1.0 second forced expiratory volumes ($FEV_{0.5}$ and $FEV_{1.0}$). The kymograph paper speed is 32 mm./second. The horizontal broken line is drawn 200 ml. below the level of maximal inspiration (I). The starting point (zero time point) for measurement (S) is at the point where the 200 ml. line crosses the expiratory curve. The 0.5 and 1.0 second vertical lines are measured from the vertical line passing through point S. The vertical distance between the 200 ml. line and the 0.5 second-spirogram crossing (A) is the 0.5 second vertical distance ($VD_{FEV_{0.5}}$). Similarly the vertical distance between the 200 ml. line and the 1.0 second-spirogram crossing (B) is the $FEV_{1.0}$ vertical distance ($VD_{FEV_{1.0}}$). With these vertical distances the actual $FEV_{0.5}$ and $FEV_{1.0}$ may be calculated (see text).

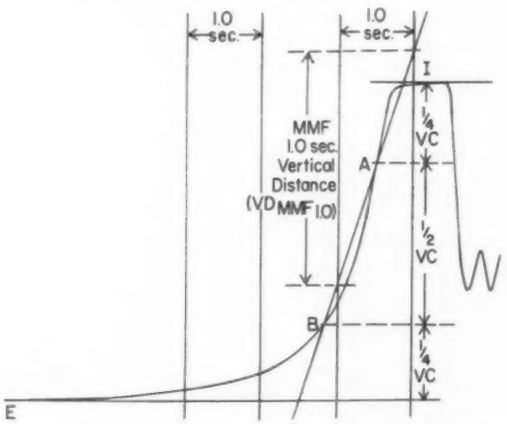


FIG. 4. Forced expiratory spirogram (FES) illustrating the measurement of the maximal mid-expiratory flow (MMF).[8] The kymograph paper speed is 32 mm./second. Two points are located on the FES: A is one-fourth of the VC vertical distance *down* from the level of maximal inspiration (I) and B is one-fourth of the VC vertical distance *up* from the level of maximal expiration (E). A line is drawn through A and B to provide the slope of the MMF and is extended to intersect two adjacent one-second vertical time lines. The vertical distance between these two points of intersection is the MMF 1.0 second vertical distance ($VD_{MMF_{1.0}}$). By inserting the value for ($VD_{MMF_{1.0}}$) in formula 8, the MMF can be calculated (see text).

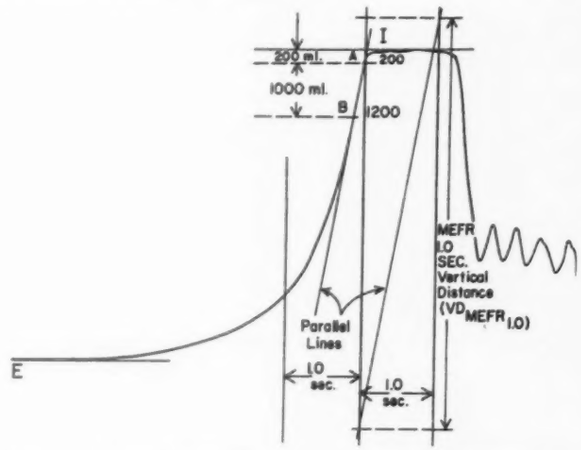


FIG. 3. Forced expiratory spirogram (FES) illustrating measurement of the maximal expiratory flow rate (MEFR). The kymograph paper speed is 32 mm./second. Two points are located on the FES, one at the 200 ml. crossing point (A) and the second at 1,200 ml. crossing point (B). A line is drawn through these two points to provide the slope of the MEFR. In order to measure this slope, a parallel line is drawn to intersect two adjacent time lines one second apart. The vertical distance between the two points of intersection is the MEFR 1.0 sec. vertical distance ($VD_{MEFR_{1.0}}$). By inserting the value for $VD_{MEFR_{1.0}}$ in formula 7, the MEFR can be calculated (see text).

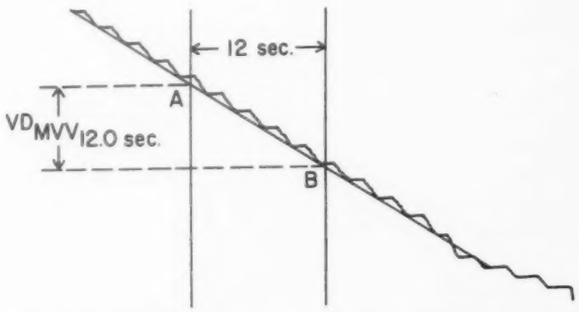


FIG. 5. Measurement of MVV_F from the ventilograph tracing. The kymograph paper speed is 32 mm./twelve seconds. The diagonal line is drawn to connect the lower points of the steps made by the ventilograph pen. The interval between the vertical time lines equals twelve seconds. The intersection of the diagonal line with two adjacent time lines (points A and B) provides the ventilograph pen twelve-second vertical distance ($VD_{\text{Vent Pen } 12.0 \text{ seconds}}$). By inserting the value for ($VD_{\text{Vent Pen } 12.0 \text{ seconds}}$) in formula 9, MVV_F may be calculated.

spirometer bell factor (SBF) to convert the millimeters of vertical excursion to milliliters of gas volume. For most 13.5 L. Collins respirometers 1 mm. of pen excursion represents 41.27 ml. change in volume. The SBF for these instruments, therefore, is 41.27.

All gas volumes are measured at ambient tempera-

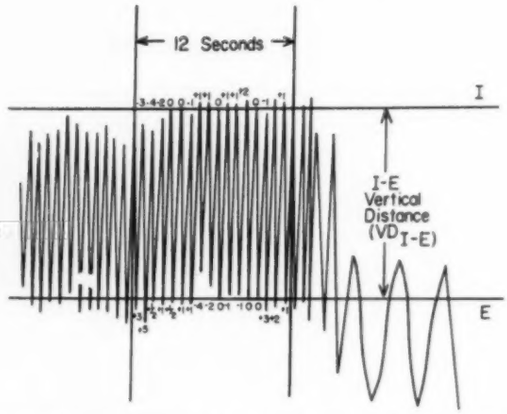


FIG. 6. Measurement of the main pen MVV spirographic tracing. The kymograph paper speed is 32 mm./12 second so that the interval between the vertical time lines is twelve seconds. Horizontal lines I and E are drawn through the greatest number of inspiratory and expiratory peaks. The I-E distance ($VD_{I\text{-}E}$) is multiplied by the number of breaths in the twelve-second interval ($f_{12.0}$). The resulting product ($VD_{I\text{-}E} \times f_{12.0}$) is corrected by *adding* to it the sum of the deviations in mm. of the peaks lying *outside* I and E (indicated by plus signs), and then subtracting the sum of the deviations in mm. of peaks lying *inside* I and E (indicated by minus signs). This corrected product represents the total mm. excursion of the main recording pen for the twelve-second period ($VD_{MVV\ 12.0\ seconds}$). By inserting the value for $VD_{MVV\ 12.0\ seconds}$ in formula 10, the MVV_F may be calculated (see text).

ture and pressure, saturated with water vapor (ATPS) but are converted to body temperature and pressure, saturated with water vapor (BTPS) by applying a BTPS conversion factor (BTPS factor) [*24*].

Vital Capacity and Inspiratory Vital Capacity. The vital capacity is represented on the spirographic tracing (Fig. 1A) by the vertical distance between the level of maximal inspiration and maximal expiration (VD_{VC}). The vital capacity in liters is calculated by the following formula:

$$VC_{BTPS}, \text{ liters} = \frac{VD_{VC} \times SBF \times BTPS \text{ factor}}{1000} \quad (1)$$

Similarly, the inspiratory vital capacity is represented in the spirogram (Fig. 1B) by the vertical distance between the level of the maximal expiration and maximal inspiration (VD_{IVC}). The inspiratory vital capacity in liters is calculated by the following formula:

$$IVC_{BTPS}, \text{ liters} = \frac{VD_{IVC} \times SBF \times BTPS \text{ factor}}{1000} \quad (2)$$

These calculations may be simplified by constructing tables applicable to the particular instrument and average barometric pressure of the area so that the millimeters of vertical distance together with the temperature can be used in the table to provide direct reading of the VC_{BTPS} or IVC_{BTPS} values in liters [*25*].

0.5 Second and 1.0 Second Forced Expiratory Volumes ($FEV_{0.5}$ and $FEV_{1.0}$). The forced expiratory volume as defined by Gandevia and Hugh-Jones [*22*] is that volume of gas expired between two stated time intervals during the performance of the forced vital capacity. Thus, $FEV_{1.0\text{-}2.0}$ would represent the volume of gas expired between the 1.0 second point and the 2.0 second point. Where the initial time is the zero or starting point, the zero subscript is dropped. Thus, the 1.0 second forced expiratory volume is written $FEV_{1.0}$ instead of $FEV_{0\text{-}1.0}$.

In this study the failure of some subjects to produce a sharp onset of the forced expiratory spirogram suggested that more reproducible measurements could be obtained if the starting point for the $FEV_{0.5}$ and the $FEV_{1.0}$ was arbitrarily set 200 ml. below peak inspiration (S in Figure 2). The horizontal distance corresponding to 0.5 second (16 mm.) and 1.0 second (32 mm.) is measured with a vertical lined ruler [*25,26*] and marked on the expiratory tracing. The vertical distance between the 200 ml. point and the 0.5 second point represents the $VD_{FEV_{0.5}}$ and the vertical distance between the 200 ml. point and the 1.0 second point represents the $VD_{FEV_{1.0}}$. (Fig. 2.) These vertical distances are converted to liters, BTPS, by the following formulas:

$$FEV_{0.5_{BTPS}}, \text{ liters} = \frac{VD_{FEV_{0.5}} \times SBF \times BTPS \text{ factor}}{1000} \quad (3)$$

$$FEV_{1.0_{BTPS}}, \text{ liters} = \frac{VD_{FEV_{1.0}} \times SBF \times BTPS \text{ factor}}{1000} \quad (4)$$

The $FEV_{0.5}$ and $FEV_{1.0}$ are also expressed as a percentage of the total forced vital capacity:

$$FEV_{0.5}, \% \text{ of total} = \frac{FEV_{0.5}}{FVC} \times 100 \quad (5)$$

$$FEV_{1.0}, \% \text{ of total} = \frac{FEV_{1.0}}{FVC} \times 100 \quad (6)$$

Maximal Expiratory Flow Rate (MEFR) [*16-18*]. Measurement is begun at the same 200 ml. point used as the starting point for $FEV_{0.5}$ and $FEV_{1.0}$ (A in Figure 3) and a second point on the forced expiratory spirogram which represents the next 1,000 ml. of expired gas (B in Figure 3). The line connecting the 200 ml. and 1,200 ml. points (or a line parallel to it) is extended to cross two adjacent vertical time lines on the kymograph paper. Since these vertical lines are one second apart, the vertical distance between the intersection represents the volume expired in one second. This one-second vertical distance ($VD_{MEFR_{1.0}}$) is then converted into liters of gas at BTPS by the fol-

lowing formula:

$$MEFR_{BTPS}, \text{ liters/sec.} = \frac{VD_{MEFR_{1.0}} \times SBF \times BTPS \text{ factor}}{(1000)} \quad (7)$$

Maximal Mid-Expiratory Flow (MMF) [19]. The measurement is illustrated in Figure 4. The vertical distance between maximal inspiration and maximal expiration is measured. Two points are located on the curve, one of which is one-fourth the vertical distance down from the level of maximal inspiration (A in Figure 4) and the other one-fourth of the vertical distance up from the level of maximal expiration (B in Figure 4). The middle half of the forced expiratory spirogram volume is thus identified. A line connecting A and B is extended to cross the adjacent one-second vertical lines on the kymograph paper. The vertical distance between these one-second intersects ($VD_{MMF_{1.0}}$) is converted to liters/second BTPS by a formula similar to (7) above:

$$MMF_{BTPS}, \text{ liters/sec.} = \frac{VD_{MMF_{1.0}} \times SBF \times BTPS \text{ factor}}{1000} \quad (8)$$

Maximal Voluntary Ventilation, Free. Two methods of measurement have been used. The first employs the record of the Reichert ventilograph pen [27]. This pen moves upward only during inspiration and transcribes a horizontal record during expiration. The ventilograph pen records the inspiratory volumes only in a fixed ratio to the main recording pen. This ratio is the ventilograph factor (VF). For most 13.5 L. respirometers this ratio is approximately 1:11, but the VF should be checked for each instrument. Thus an inspiratory effort recording 11 mm. on the main recording pen will result in a 1 mm. upward deflection of the ventilograph pen. In this manner the volumes of successive inspirations are continuously summed. Measurement of this ventilograph tracing is illustrated in Figure 5. The slope of the ventilograph tracing is obtained by drawing a line which connects the lower points of the step pattern. As this line crosses two adjacent twelve-second vertical lines on the kymograph paper (since the slow speed is used for the MVV_F), the vertical distance between the two points of crossing (indicated by A and B in Figure 5) is measured. This is termed the ventilograph pen twelve-second vertical distance ($VD_{Vent\ Pen_{12.0\ sec.}}$). From this measurement the MVV_F is calculated by the following formula:

$$MVV_{F_{BTPS}}, \text{ L./min.} = \frac{VD_{Vent\ Pen_{12.0\ sec.}} \times VF \times SBF \times BTPS \text{ factor} \times 5}{1000} \quad (9)$$

TABLE II
DISTRIBUTION OF SUBJECTS BY FIVE-YEAR AGE GROUPS

Age Group (yr.)	No. of Subjects
18–19	2
20–24	41
25–29	90
30–34	66
35–39	82
40–44	79
45–49	41
50–54	36
55–59	12
60–64	14
65–66	5
Total	468

where

VF = ventilograph factor. This is 11.09 for most Collins 13.5 L. respirometers but should be measured for each instrument.

5 = constant for converting liters/twelve seconds to liters/minute.

The second method of measuring the MVV_F involves the direct measurement of the tracing obtained from the main recording pen (Fig. 6), in which the inspiratory and expiratory peaks are shown. One horizontal line (I in Figure 6) is drawn through most of the inspiratory peaks and a second (E in Figure 6) through most of the expiratory points. This vertical distance between I and E ($VD_{I\text{-}E}$) is multiplied by the number of breaths in the twelve-second period estimating the nearest fractional portion of the final breath. The sum of deviations of peaks lying *outside* the horizontal lines (as indicated by plus signs in Figure 6) is added to the product of $VD_{I\text{-}E} \times$ the number of breaths. The sum of the deviations lying *within* the horizontal lines (as indicated by minus signs in Figure 6) are subtracted from the above sum. This results in a total millimeter excursion of the main recording pen for the twelve-second period ($VD_{MVV_{12.0\ sec.}}$). From this millimeter value the MVV_F may be calculated by the following formula:

$$MVV_{F_{BTPS}}, \text{ L./min.} = \frac{VD_{MVV_{12.0\ sec.}} \times SBF \times BTPS \text{ factor} \times 5}{1000} \quad (10)$$

RESULTS

A total of 468 male subjects were studied in fifteen different hospitals. The subjects ranged in age from eighteen to sixty-six, with a mean age of 37.3 years. The distribution of the subjects by age is shown in Table II. Table III presents the mean values and the standard deviations for

TABLE III
PHYSICAL CHARACTERISTICS AND PULMONARY FUNCTION MEASUREMENTS
Mean Values and Standard Deviations

Measurement		Unit	Mean	St. Dev.	No. of Subjects
1. Age		yr.	37.3	10.5	468
2. Height		in.	69.5	2.9	468
		cm.	176.5	7.4	
3. Weight		lb.	170.5	24.5	468
		kg.	77.5	11.1	
4. BSA		M^2	1.94	0.16	468
5. Chest circumference	Maximal inspiration	in.	39.2	3.3	215
		cm.	99.5	8.3	
6.	Expansion	in.	2.5	1.1	
		cm.	6.3	2.8	
7. Chest antero-posterior diameter	Maximal inspiration	in.	9.4	4.0	175
		cm.	23.9	10.3	
8.	Expansion	in.	1.0	0.5	
		cm.	2.6	1.2	
9. VC (standing)		liters	4.81	0.76	468
10. IVC (standing)		liters	4.90	0.80	238
11. $FEV_{0.5}$		liters	2.86	0.60	158
12.		% of VC	58.0	10.0	
13. $FEV_{1.0}$		liters	3.93	0.67	389
14.		% of VC	82.0	8.7	
15. MEFR		L./sec.	7.02	2.4	369
16. MMF		L./sec.	4.49	1.3	376
17.	Total volume	L./min.	164.0	34.0	464
18. MVV_F	Breathing frequency	f/min.	100.0	35.0	308
19.	Tidal volume	liters	1.88	0.74	248

each of the nineteen measurements. It should be noted that the variation in the number of subjects reflects the fact that certain measurements were not available for some.

An electronic data processing machine (IBM "650")* was used to develop a product-moment correlation (r) matrix based on the nineteen parameters available. Each of the nineteen measurements was correlated with the other eighteen measurements. This correlation matrix is shown in Table IV. To aid in understanding this matrix, we have arbitrarily indicated by bold face type those correlation coefficients greater than ± 0.30.

The first eight items in Table IV are anthropomorphic measurements, whereas the remaining eleven are derived from pulmonary function testing. Age does not correlate highly with any of the anthropomorphic measurements made, but does show consistent negative correlations with all of the pulmonary function measurements. Height, weight and BSA are interrelated; this is reflected in the positive correlations found between them. It is of interest that the BSA shows a significantly higher correlation with weight than with height.

Height demonstrates consistent positive correlations with vital capacity, both VC and IVC. Height also correlates positively with both forced expiratory volumes ($FEV_{0.5}$ and $FEV_{1.0}$) and with the MVV_F, although lower than with the vital capacity.

In this study height demonstrates a consistently higher correlation with all the measurements of pulmonary function than does BSA. Weight shows little or no correlation with any of the pulmonary function measurements. Age has a low negative correlation with height.

The chest circumference measurement with maximal inspiration correlates positively with both weight and BSA, as might be expected, but shows poor correlation with the pulmonary function values. Chest expansion, however, (particularly circumferential expansion) relates positively with most of the pulmonary function measurements.

An almost perfect correlation is found between VC and IVC. Both of these measurements show their highest positive correlations with $FEV_{1.0}$ and exhibit slightly lower correlations with $FEV_{0.5}$ and MVV_F.

The $FEV_{0.5}$ and $FEV_{1.0}$ are highly related and both show strong positive correlations with MMF and MVV_F. A difference is found between these two measurements in that the $FEV_{0.5}$ shows a higher positive relationship with the MEFR than does the $FEV_{1.0}$.

Since age and height consistently showed the highest correlations with VC, $FEV_{0.5}$, $FEV_{1.0}$ and MVV_F, these two parameters were chosen for deriving prediction formulas for these four pulmonary function measurements. Construction of such formulas was accomplished by cal-

* This instrument was made available through the courtesy of Dr. A. Bernard Drought, Dean of Engineering and Director of the Computer Center of Marquette University, Milwaukee, Wisconsin.

TABLE IV

PHYSICAL CHARACTERISTICS AND PULMONARY FUNCTION MEASUREMENTS

Correlation Coefficients

Measurement		1. Age	2. Height	3. Weight	4. BSA	5. Chest Circumference: Maximal Inspiration	6. Chest Circumference: Expansion	7. Chest Anteroposterior Diameter: Maximal Inspiration	8. Chest Anteroposterior Diameter: Expansion	9. VC (expiratory)	10. IVC (inspiratory)	11. $FEV_{0.5}$: Liters	12. $FEV_{0.5}$: % of VC	13. $FEV_{1.0}$: Liters	14. $FEV_{1.0}$: % of VC	15. MEFR	16. MMF	17. MVV_F: L./min.	18. MVV_F: Breathing Frequency	19. MVV_F: Tidal Volume
1. Age		1.0	−0.17	...	...	...	−0.28	...	−0.22	**−0.40**	**−0.36**	**−0.46**	−0.20	**−0.50**	−0.23	...	**−0.44**	**−0.44**	−0.12	−0.16
2. Height		−0.17	1.0	**0.54**	**0.76**	0.19	0.19	0.21	...	**0.56**	**0.63**	**0.31**	...	**0.47**	...	...	0.21	**0.36**	...	...
3. Weight		...	**0.54**	1.0	**0.93**	**0.64**	...	...	...	0.26	0.26	...	...	0.20	...	...	...	0.12	...	...
4. BSA		...	**0.76**	**0.93**	1.0	**0.55**	...	...	..	**0.41**	**0.44**	0.21	...	**0.32**	...	...	0.23	0.23	...	0.17
5. Chest circumference	Maximal inspiration	...	0.19	**0.64**	**0.55**	1.0	...	...	...	0.15	...	...	...	...	...	0.17	0.21	...	...	...
6	Expansion	−0.28	0.19	...	...	...	1.0	**0.46**	0.25	**0.37**	**0.40**	**0.43**	...	**0.52**	0-26	...	0.30	0.28	0.15	...
7. Chest anteroposterior diameter	Maximal inspiration	...	0.21	...	...	...	**0.46**	1.0	...	0.17	0.18	...	...	...	...	...	...	...	...	...
8.	Expansion	−0.22	...	...	...	...	0.25	...	1.0	**0.31**	0.27	0.22	...	0.25	...	...	...	0.23	...	...
9. VC (expiratory)		**−0.40**	**0.56**	0.26	**0.41**	0.15	**0.37**	0.17	**0.31**	1.0	**0.98**	**0.63**	...	**0.80**	...	0.18	**0.37**	**0.56**	...	0.28
10. IVC (inspiratory)		**−0.36**	**0.63**	0.26	**0.44**	...	**0.40**	0.18	0.27	**0.98**	1.0	**0.61**	...	**0.81**	...	0.30	**0.36**	**0.61**	...	0.29
11. $FEV_{0.5}$	liters	**−0.46**	**0.31**	...	0.21	...	**0.43**	...	0.22	**0.63**	**0.61**	1.0	**0.64**	**0.87**	**0.58**	**0.61**	**0.74**	**0.57**	...	**0.36**
12.	% of VC	−0.20	...	...	...	...	...	...	...	...	...	**0.64**	1.0	0.28	**0.77**	**0.52**	**0.56**	...	...	0.19
13. $FEV_{1.0}$	liters	**−0.50**	**0.47**	0.20	**0.32**	...	**0.52**	...	0.25	**0.80**	**0.81**	**0.87**	0.28	1.0	**0.46**	0.17	**0.68**	**0.60**	...	**0.32**
14.	% of VC	−0.23	...	...	...	...	0.26	...	...	...	...	**0.58**	**0.77**	**0.46**	1.0	**−0.42**	0.21	0.20	...	0.15
15. MEFR		...	...	...	...	0.17	...	...	...	0.18	0.30	**0.61**	**0.52**	0.17	**−0.42**	1.0	0.18	−0.26	...	0.22
16. MMF		**−0.44**	0.21	...	0.23	0.21	0.30	...	...	**0.37**	**0.36**	**0.74**	**0.56**	**0.68**	0.21	0.18	1.0	0.15	...	0.30
17. MVV_F	L./min.	**−0.44**	**0.36**	0.12	0.23	...	0.28	...	0.23	**0.56**	**0.61**	**0.57**	...	**0.60**	0.20	−0.26	0.15	1.0	0.18	**0.36**
18.	Breathing frequency	−0.12	...	...	...	...	0.15	...	...	...	...	...	...	...	...	...	...	0.18	1.0	**−0.71**
19.	Tidal volume	−0.16	...	...	0.17	...	...	...	...	0.28	0.29	**0.36**	0.19	**0.32**	0.15	0.22	0.30	**0.36**	**−0.71**	1.0
Number of subjects (N)		468	468	468	468	215	215	175	175	468	238	158	158	389	389	369	376	464	308	248

NOTE: Correlation coefficients greater than ±0.30 are shown in bold face type to emphasize the higher correlations.
... = Correlation is not statistically significant ($p > 0.01$).

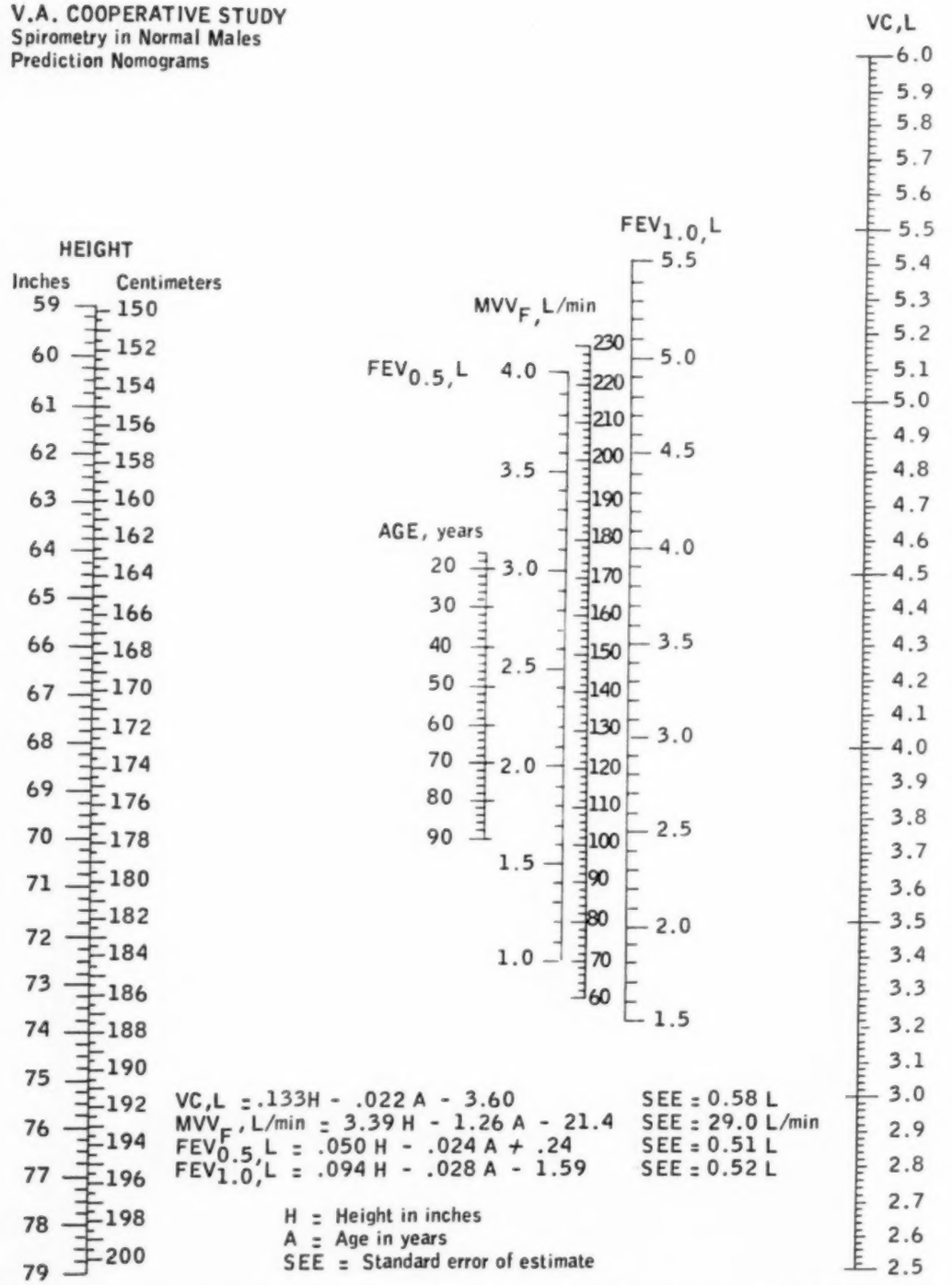


FIG. 7. Nomogram for prediction of VC, $FEV_{0.5}$, $FEV_{1.0}$ and MVV_F from age and height. Points representing the observed heights in inches (or centimeters) and the observed age in years are located on the height and age scales. A straight line passing through these points intersects points on the $FEV_{0.5}$, $FEV_{1.0}$, MVV_F, and VC scales corresponding to their predicted values.

culating the multiple correlations (R) for age and height and using the resulting β weights in combination with the sample means and standard deviation to derive appropriate equations.

These prediction formulas along with their respective "R" values* and standard errors of estimate (S.E.E.) are as follows:

$$\left.\begin{aligned} \text{VC, liters} &= .052\ H_{cm} - .022\ A - 3.60 \\ &= (.133\ H_{in} - .022\ A - 3.60) \end{aligned}\right\} \begin{matrix}(R = .64) \\ (S.E.E. = .58)\end{matrix} \quad (11)\ (12)$$

$$\left.\begin{aligned} FEV_{0.5},\ \text{liters} &= .020\ H_{cm} - .024\ A + .24 \\ &= (.050\ H_{in} - .024\ A + .24) \end{aligned}\right\} \begin{matrix}(R = .52) \\ (S.E.E. = .51)\end{matrix} \quad (13)\ (14)$$

$$\left.\begin{aligned} FEV_{1.0},\ \text{liters} &= .037\ H_{cm} - .028\ A - 1.59 \\ &= (.094\ H_{in} - .028\ A - 1.59) \end{aligned}\right\} \begin{matrix}(R = .63) \\ (S.E.E. = .52)\end{matrix} \quad (15)\ (16)$$

$$\left.\begin{aligned} MVV_F,\ \text{L./min.} &= 1.34\ H_{cm} - 1.26\ A - 21.4 \\ &= (3.39\ H_{in} - 1.26\ A - 21.4) \end{aligned}\right\} \begin{matrix}(R = .53) \\ (S.E.E. = .29)\end{matrix} \quad (17)\ (18)$$

where H_{cm} = height in cm.; H_{in} = height in inches; and A = age in years.

For convenience in determining the predicted values for these four measurements, a combined prediction nomogram has been prepared so that in a single operation the predicted normal values for VC, $FEV_{0.5}$, $FEV_{1.0}$ and MVV_F all can be read directly from the appropriate scales. (Fig. 7.) This nomogram checks with the calculated values with an error of less than 1 per cent.

The addition of circumferential chest expansion increased the precision of the predictions for VC, $FEV_{0.5}$ and $FEV_{1.0}$ in these normal subjects. Since those diseases which will impair the ventilatory parameters also will impair chest expansion, the addition of chest expansion to the prediction formulas would not be helpful in providing predicted normal values for patients with pulmonary disease. These formulas may be useful, however, if applied to large surveys of essentially normal men. These formulas together with their "R" values and standard errors of estimate are:

$$\text{VC, liters} = .049\ H_{cm} + .059\ CE_{cm} - .018\ A - 3.57\ (R = .67, S.E.E. = .56) \quad (19)$$

$$FEV_{0.5},\ \text{liters} = .016\ H_{cm} + .066\ CE_{cm} - .019\ A + .315\ (R = .59, S.E.E. = .48) \quad (20)$$

$$FEV_{1.0},\ \text{liters} = .032\ H_{cm} + .092\ CE_{cm} - .022\ A - 1.54\ (R = .72, S.E.E. = .46) \quad (21)$$

Chest expansion did not improve the prediction formula for the MVV_F.

The correlations of MEFR with the anthropomorphic measurements were so small that useful prediction formulas could not be derived. The values obtained for this measurement suggest that a lower limit of normal for the MEFR which would encompass the twenty to sixty-five year age range in males is 3.3 L./second (200 L./minute).

The MMF shows a negative correlation with age and a low positive correlation with height. However, these are of insufficient magnitude to furnish an adequate prediction formula. As with the MEFR, the values obtained for the MMF suggest that the lower limit of normal for males in the twenty to sixty-five year age range is 1.79 L./second (107 L./minute).

TABLE V
VALIDITY COEFFICIENTS FOR THE VETERANS ADMINISTRATION-ARMY COOPERATIVE STUDY PREDICTION FORMULAS

Measurement	Veterans Administration-Army Cooperative Study "R"	Milwaukee Industrial Workers [29] "r"	Miller, Johnson and Wu [30,31] "r"
VC	0.64	0.73	0.83
$FEV_{0.5}$	0.52	0.54	0.66
$FEV_{1.0}$	0.63	0.63	0.70
MVV_F	0.53	*	0.56
No. of subjects	468	514	72

* Not available.

After a prediction formula has been constructed, it can be validated by applying this formula to a comparable but independent group and correlating the predicted and observed values. This procedure has been accomplished by applying the formulas derived from this study to data obtained in a separate study of 514 normal male Milwaukee industrial workers [29] for VC, $FEV_{0.5}$ and $FEV_{1.0}$ and calculating a correlation coefficient (r) between the predicted and observed values.

Through the courtesy of Dr. W. F. Miller, we have been fortunate in obtaining the original data collected by Miller, Johnson and Wu [30,31] in connection with their study of the

* Where more than one variable is present, multiple correlation (R) is used [28].

TABLE VI

VALIDITY OF VARIOUS PREDICTION FORMULAS FOR VITAL CAPACITY WHEN APPLIED TO COOPERATIVE STUDY DATA

Number of Subjects (N) = 468

Investigator	Prediction Formula	Values as Applied to Cooperative Study Data			
		"r"	Predicted Mean (L.)	Observed Mean (L.)	Predicted Mean Minus Observed Mean (L.)
West [5]	VC, L. = 2.5 × M^2 BSA	0.39	4.84	4.81	+0.03
West [5]	VC, ml. = 25 × H_{cm}	0.51	4.42	4.81	−0.39
Hewlitt and Jackson [6]	VC, L. = 2.9 × M^2 BSA − 1	0.39	4.61	4.81	−0.20
Myers [7]	VC, ml. = W_{lb} × 21.2 + 1168	0.26	4.78	4.81	−0.03
Baldwin, Cournand and Richards [12] (supine)	VC, ml. = [27.63 − (.112A)] H_{cm}	0.58	4.14	4.81	−0.67
Miller, Johnson and Wu [30]	VC, L. = (.135 H_{in} − 4.15) × 1 − .0054(A − 20)	0.60	4.75	4.81	−0.06
Bateman [32]	VC, ml. = 873 $(H_M)^3$	0.51	4.84	4.81	+0.03
Hepper, Fowler and Helmholz [33]	VC, L. = .9 $(H_M)^3$	0.51	4.98	4.81	+0.17
Veterans Administration-Army Cooperative Study	VC, L. = .052 H_{cm} − .022A − 3.60	0.64*	4.81*	4.81*	*

NOTE: VC = Vital capacity.
r = Correlation coefficient.
W_{lb} = Weight in pounds.
A = Age in years.
M^2 BSA = Square meters, body surface area.
H_{cm} = Height in centimeters.
H_{in} = Height in inches.
H_M = Height in meters.

* The multiple correlation coefficient is given here for comparison with the other correlation values. The mean values are identical because they arise from the same data.

relationship between maximal breathing capacities and elements of the forced vital capacity.

The application of our prediction formulas to these two groups of male subjects yields validity coefficients (r) which are presented in Table v. In all cases these validity coefficients are equal to or greater than the multiple correlation (R) obtained from the original cooperative study data.

Of considerable interest is the application of prediction formulas reported in the literature to the present cooperative study data. The "r" values and the differences between the calculated and observed mean values are shown in Tables VI and VII.

It should be emphasized that the "r" value is of greater importance in evaluating such prediction formulas. The difference between the predicted and observed mean values (predicted mean minus observed mean in Tables VI and VII) reflects the difference on which the formulas were based. Thus, the predicted and observed

TABLE VII

VALIDITY OF VARIOUS PREDICTION FORMULAS FOR MAXIMAL VOLUNTARY VENTILATION, FREE (MVV_F) WHEN APPLIED TO COOPERATIVE STUDY DATA

Number of subjects (N) = 464

Investigator	Prediction Formula	Values as Applied to Cooperative Study Data			
		"r"	Predicted Mean (L./min.)	Observed Mean (L./min.)	Predicted Mean Minus Observed Mean (L./min.)
Baldwin, Cournand and Richards [12]	$MVV_{F.\ L/min} = (86.5 - .522A) \times M^2\ BSA$	0.42	130	164	−34
Wright and others [34]	$MVV_{F.\ L/min} = 228 - 1.82A$	0.39	160	164	−4
Motley [35]	$MVV_{F.\ L/min} = (97 - .5A) \times M^2\ BSA$	0.25	150	164	−14
Needham, Rogan and McDonald [36]	$MVV_{F.\ L/min} = 40M^2\ BSA - 1.1A + 94$	0.35	130	164	−34
Miller, Johnson and Wu [31]	$MVV_{F.\ L/min} = (109 - .5A) \times M^2\ BSA$	0.23	171	164	+7
Veterans Administration-Army Cooperative Study	$MVV_{F.\ L/min} = 1.34\ H_{cm} - 1.26A - 21.4$	0.53*	164*	164*	*

NOTE: MVV_F = Maximum voluntary ventilation, free (termed by the various prior investigators Maximum Breathing Capacity).
A_2 = Age in years.
M^2 BSA = Square meters, body surface area.
H_{cm} = Height in centimeters.

* The multiple correlation coefficient is given here for comparison with the other correlation values. The mean values are identical because they arise from the same data.

means can be made to agree by simply adding a constant to either formula. The correlation coefficient (r) is independent of the mean and accurately reflects the adequacy of the prediction formula.

COMMENTS

The results of the present study as they pertain to the vital capacity are in complete accord with Hutchinson's findings reported in 1846. It is surprising that in the extensive literature concerned with vital capacity measurements, there is usually only a passing reference to this pioneer investigator who not only originated and defined the "vital capacity," and clearly understood its importance, but also devised the spirometer for its measurement.

The data presented in this report are derived from a group of fifteen clinical pulmonary function laboratories—the same laboratories which are engaged in patient evaluation. These data, therefore, represent studies carried out at the hospital level and not in special research laboratories with refined and time-consuming technics.

The first problem faced by the cooperative study group was the definition of criteria for defining a normal subject for pulmonary function testing. The criteria listed under "Selection of Subjects" were those ultimately agreed upon by the various participants.

Early in the discussion of methods the question was raised as to the fidelity with which the spirometer would record rapid breathing pat-

terns. This question resulted in the investigations by Stead and Wells [*37,38*] of the physical characteristics of spirometers. These studies led to the development of a new spirometer (Stead-Wells) with a lightweight direct-writing plastic bell and a reduced spirometer dead space. A subsequent investigation has compared the Stead-Wells spirometer with the 13.5 and 9 L. metal spirometers in normal subjects and in patients [*39*]. This study indicated that the 13.5 L. metal bell instrument recorded values which were not materially different from those of the Stead-Wells spirometer if the breathing frequency did not exceed 110/minute.

The need for devising uniform terms for the ventilatory function measurements has been apparent for several years, particularly when so many new workers are entering the field. The "Pappenheimer Committee" [*23*] made a lasting contribution by their standardization of terms for the compartments of the lung. The report of Gandevia and Hugh-Jones [*22*] would appear to offer similar benefits. This terminology seems sufficiently explicit to warrant its adoption on a more general basis.

One important exception has been made in relation to the Gandevia and Hugh-Jones terminology which is primarily a difference in measuring technic. The $FEV_{0.5}$ and $FEV_{1.0}$ measurements as made *in this study* were *not* from the *onset* of the forced expiratory spirogram but from a point *200 ml. below this onset* of the FES. The terms $FEV_{0.5}$ and $FEV_{1.0}$ as used in this report, therefore, are not in strict accord with the terminology of Gandevia and Hugh-Jones. This method of measurement was established early in the study to locate a more precise point of onset for the FES. For this study all the data were obtained using this 200 ml. starting point. Presently, however, some of the members of the cooperative study group, after comparing the data with other published reports, have questioned the necessity of using the 200 ml. mark as the starting point for the $FEV_{0.5}$ and $FEV_{1.0}$. In those instances in which the forced expiratory spirogram has a sharp onset, precise measurement of $FEV_{0.5}$ and $FEV_{1.0}$ presents no difficulty. When the onset of the FES presents a gradual curve, determination of the starting point can be made by extrapolating the steepest linear portion of the FES to its intersect with the horizontal line across the inspiratory plateau. (Fig. 3.)

In view of the recent acceptance of the MEFR as a clinical measurement, it is important to point out that the MEFR showed the greatest variance of any of the spirometric measurements in this study. This variance was so great that no significant linear correlation with either age or height could be demonstrated, and the MEFR actually showed an inverse relationship with the MVV_F. The extreme variability of the MEFR in normal subjects makes it questionable whether this measurement can reliably detect minimal or slight impairment of ventilatory function. However, the studies of abnormal persons may indicate the value of the MEFR in indicating changes not measured by other fast expiratory maneuvers.

For the various pulmonary function measurements, correlation with height was consistently higher than with either weight or body surface area. Although in the Dubois [*21*] formula for BSA, height is almost twice as important as weight, the wide range of weights in adults of the same height nullifies the importance of height and allows the weight to be of primary importance in determining the BSA. This finding suggests both theoretically and practically that the use of BSA in prediction formulas for spirometric measurements lessens the accuracy. If the prediction formula was derived from a population sample, neither overweight nor underweight, the use of BSA would be relatively reliable. In practice, however, such prediction formulas would be applied to the general adult population in which weight varies to a far greater extent than does height.

It should be noted that four of the five formulas for the prediction of the MVV_F in Table VI employ the BSA rather than height. The fifth formula is based upon age alone. It is difficult to understand why the MVV_F prediction formulas heretofore have not made use of height in place of BSA. The two most detailed derivations of MVV_F prediction formulas, those of Baldwin, Cournand and Richards [*12*], and of Needham, Rogan and McDonald [*36*], both show higher correlations of MVV_F with height than with BSA. This discrepancy is even greater in females.

After prediction formulas were derived, it was possible to accomplish cross validation rapidly because of the availability of an electronic computer. Whereas previous investigators have recognized the importance of careful statistical analysis of pulmonary function test data, the time-consuming nature of the statistical technics has made cross validation most difficult.

The availability of the electronic computer together with data from independent studies has facilitated cross validation.

By comparing the validity coefficients (r) of the Veterans Administration-Army prediction formulas as presented in Table v with the validity coefficients for the other prediction formulas as given in Table vi and Table vii it can be seen that the Veterans Administration-Army prediction formulas consistently demonstrate the highest cross-validation coefficients.

Although prediction formulas for spirometric measurements are presented for convenience in clinical use, it should be emphasized that such formulas include large elements of error due to variance. This is illustrated in our prediction formulas by the relatively large size of the standard errors of estimate. In applying these formulas to a clinical problem, one should remember that the true normal value for a person may be as much as 2 S.E.E. below the figure obtained from the prediction formula ($p < .025$ for one-half of the normal distribution).

In this study, methods of spirometric measurement and calculation of the volumes and flows have been presented in considerable detail in order to provide sound practical spirometric technics which can be reliably applied in the clinical situation.

SUMMARY

1. A standardized procedure for clinical spirometry is described which was formulated by a Veterans Administration-Army Cooperative Group for pulmonary function testing.

2. Spirometric studies of 468 normal men were contributed by fifteen participating pulmonary function laboratories. The nineteen parameters measured were tabulated and analyzed with the aid of an electronic computer.

3. Mean values and standard deviations were calculated for each measurement.

4. A product-moment correlation matrix was constructed which shows the relationship of each measurement to the other eighteen measurements.

5. Of the several physical measurements, age and height showed the highest correlations with VC, $FEV_{0.5}$, $FEV_{1.0}$ and MVV_F. Regression equations for these ventilatory measurements were constructed upon age and height.

6. A nomogram is presented which can be used to obtain simultaneously the predicted normal values for VC, $FEV_{0.5}$, $FEV_{1.0}$ and MVV_F.

7. Cross validation of the prediction formulas with two sets of independent data demonstrates that the Veterans Administration-Army prediction formulas have retained their reliability and have the highest cross-validation coefficients of any formulas now available.

8. The weakness implicit in the use of BSA in constructing prediction formulas for spirometric measurements is discussed.

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Heat and Water Exchange in the Respiratory Tract*

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THE respiratory system relies on an elegant set of defense mechanisms to protect its internal environment. Besides filtering foreign matter and bacteria, the upper respiratory tract is able to warm and saturate inspired air so that in climates as cold as minus 100°C. air entering the alveoli has attained body temperature and is saturated with water vapor [*1*]. The ability of the upper respiratory tract to "condition" inspired air in this manner not only protects the alveolar membrane from thermal injury but also by keeping the membrane wet, permits the vital process of carbon dioxide excretion to occur with such rapidity [*2*]. This most important function of the upper respiratory tract is accounted for by the rapid exchange of heat and water between respired air and the respiratory tract mucosa. This exchange occurs with amazing speed in both directions; during inspiration air is warmed and humidified for the alveolar environment, and during expiration heat and water are reclaimed by the mucosa.

The dual ability of the respiratory tract to condition air during inspiration and to conserve heat and water during expiration is based upon physical principles of heat and water exchange that are well known to the physicist and engineer but are infrequently utilized by the physician. This aspect of pulmonary function has been sparsely reported in the medical literature [*3–5*] and there is no report to date that describes heat and water exchange as it occurs in the abnormal respiratory tract. The present report is an attempt to translate into clear terms the basic principles of heat and water exchange as they pertain to this "air conditioning" function of the normal respiratory tract. The concepts gained through an understanding of these principles are then applied to a number of clinical problems involving the respiratory tract in disease.

HEAT AND WATER EXCHANGE IN THE NORMAL RESPIRATORY TRACT

The function of the upper respiratory tract to heat inspired air was first recognized by Magendie in 1829 [*6*]. Until that time it was assumed that any warming of inspired air occurred entirely within the lung. The studies of Aschenbrandt fifty-seven years later [*7*] indicated that air inspired at 12°C. was warmed to at least 30°C. on its course to the posterior pharynx. Perwitzschky [*8*], Moritz [*1*] and Cole [*5*] extended measurements of air temperature down to the carina, demonstrating that the greatest part of the conditioning of inspired air occurred at the portal of entry where the temperature gradients were most marked. These investigators demonstrated that inspired air was warmed to body temperature long before it reached the alveoli, despite temperatures on inspiration as low as minus 100°C. and despite high rates of air flow on inspiration. Cole [*9*] showed that the mouth performed this function with an efficiency nearly equal to that of the nose.

The humidification of inspired air has been studied with equal care [*9–13*]. These studies demonstrate that the water content of inspired air increases as the air is warmed, and that it becomes saturated with water vapor (100 per cent relative humidity) at 37°C. before it enters the lungs. A number of studies have confirmed the fact that air in the lungs remains at body temperature (37°C.) fully saturated with water vapor [*10–13*].

The temperature and humidity of expired air has been studied by numerous investigators

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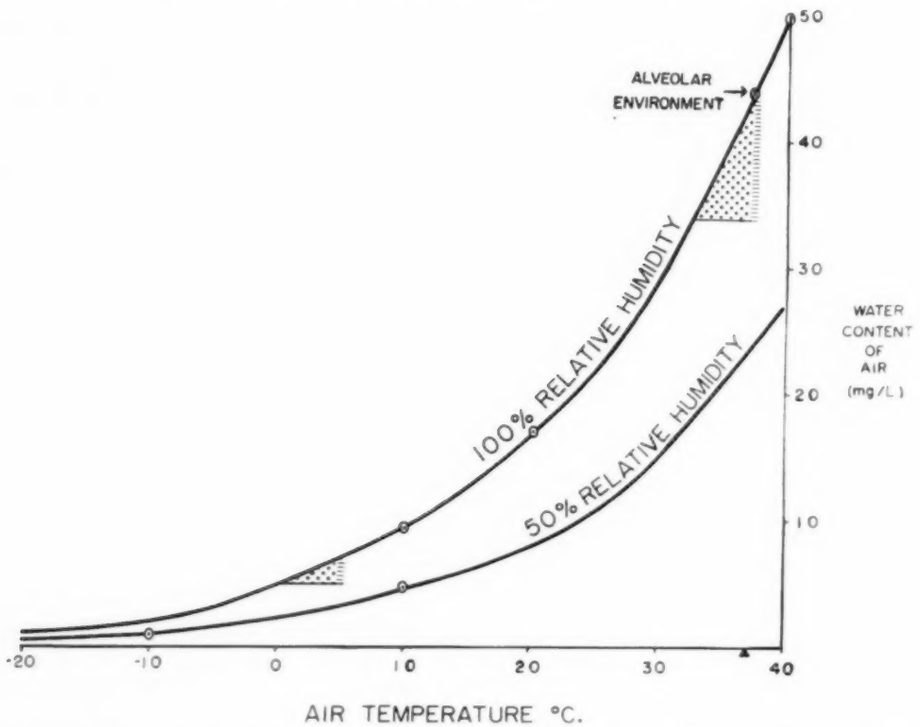


FIG. 1. Relationship of water content of air to air temperature. A comparison of the height of the stippled triangles illustrates the difference in the amount of water condensed (cross lines) when the temperature of saturated air is lowered 5° from body temperature (37°c.) and 5° from 5°c.

[*1,3,5,9–16*]. Alveolar air has been found to undergo a gradual decrease in temperature and water content during its passage out of the respiratory tract. These studies demonstrate that normal man breathing quietly in a temperate climate reduces the temperature of his alveolar air from 37° to 32°c. at the time it exits from the nose or mouth. The expired air remains saturated with water vapor during the cooling process over the expiratory route while the absolute water content decreases.

The Physical Principles of Heat and Water Exchange. Inspiratory cycle: During inspiration in temperate climates heat and water are transferred from the respiratory tract mucosa to inspired air. Heat is transferred to inspired air by means of "turbulent convection." Turbulence is the important factor which promotes the rapid transfer of heat by convection, since air conducts heat poorly, and radiation is a relatively slow means of heat exchange. The turbulence that occurs in the upper airways during quiet breathing [*16,17*] results in a large portion of respired air coming into direct contact with the respiratory tract mucosa; turbulent mixing then promotes the rapid dissipation of heat throughout the air stream. A rapid exchange of heat is therefore promoted in the upper respiratory tract where turbulence is most marked [*16*] and where the temperature gradient between mucosa and inspired air is greatest.

As inspired air is warmed by turbulent convection, water is simultaneously transferred to inspired air by evaporation from the mucosa. The capacity of inspired air to hold this water vapor increases as air is warmed. Figure 1 demonstrates this relationship, illustrating the fact that the maximum water holding capacity of air increases exponentially as air temperature increases. The progressive warming of inspired air promotes continued evaporation of water from the mucosa until an equilibrium of vapor pressure is established between mucosal water and inspired air. This equilibrium is established when inspired air is saturated with water vapor and is equal in temperature to the mucosa. The forces of evaporation and turbulent convection therefore act together to saturate air at body temperature before it enters the alveoli.

The mucosa is cooled during inspiration both by the loss of heat energy to inspired air and by the evaporation of water into inspired air. Evaporation produces cooling by transporting heat energy from mucosal water to the water vapor. This heat energy, known as the latent heat of vaporization, remains in latent form (in water vapor) until it is released by condensation. The heat energy transferred from the mucosa into water vapor therefore cools the mucosa but because the heat energy remains in latent form it does not participate in warming the inspired air. During the inspiratory phase of respiration therefore, air is warmed to body temperature by turbulent convection and saturated at this temperature by evaporation. Both turbulent convection and evaporation act to cool the mucosa. (Fig. 2.)

Expiratory cycle: The lower temperature of the mucosa produced by the cooling effects of inspired air accounts for the return of heat and water to the mucosa during expiration. According to Cole [9] the temperature of nasal mucosa is 31°C. at the end of inspiration. When the expiratory cycle begins, air that exists in the alveolar environment at 37°C. and at 100 per cent relative humidity encounters the cooler mucosa of the upper airway. Turbulent convection again promotes a temperature equilibrium between the mucosa and expired air, so that heat energy returns to the cooler mucosa. As expired air is cooled by this heat loss, the capacity of air to contain water is decreased and condensation of water vapor on the mucosa ensues. (Fig. 1.) When condensation occurs the latent heat in water vapor is released. During expiration, therefore, the mucosa recovers not only heat by turbulent convection, but also water and the latent heat in water vapor by condensation. (Fig. 2.) The mucosa is warmed and rehydrated in preparation for the next inspiration.

The normal respiratory tract thus performs a dual function in the exchange of heat and water. It conditions inspired air to protect its internal environment and it conserves heat and water during expiration. The respiratory tract mucosa is further able to adjust the amount of heat and water conserved during expiration and by this means it contributes significantly to total body heat and water balance. This heat and water balance mechanism is not controlled by the usual centers that regulate the elimination of heat and water but rather is governed by the temperature and humidity of the climate. To

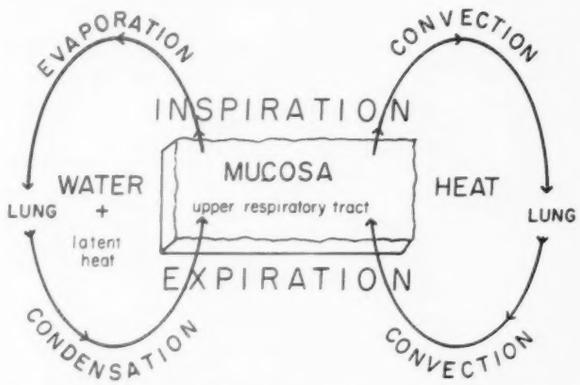


FIG. 2. Diagrammatic summary of heat and water exchange within the upper respiratory tract.

illustrate this mechanism three separate climatic conditions are selected: temperate, cold and hot. Also considered under these headings are the phenomena which enable the respiratory tract to protect itself from injury in very cold or hot environments.

Respiratory Heat and Water Exchange in Different Environments. Temperate environment: The temperature and humidity of air inspired from the environment act to regulate the amount of heat and water conserved by the normal respiratory tract. Both the temperature and humidity of the environment therefore become important considerations. Man's usual temperate environment averages 25°C. (77°F.) and roughly 50 per cent relative humidity. Relative humidity is an expression of the ratio of the actual water vapor present in air to the maximal amount of water vapor that can be contained in the air at any given temperature.* It is recorded as a percentage of the maximum capacity (saturation). This maximum capacity, as Figure 1 demonstrates, increases exponentially as air temperature increases. The less well known value, absolute humidity, refers to the actual volume of water present in a given quantity or volume of air.†

It may be noted in Figure 1 that air of 50 per cent relative humidity at 25°C. has approximately 10 mg. of molecular water vapor per liter of air. At 37°C. and 100 per cent relative humidity (the alveolar environment) there are 44 mg. of water (as molecular vapor) per liter of air. The amount of water that must be added to a

* More precisely expressed as the ratio of the partial pressure of water in air to the vapor pressure (saturated pressure) of water in air at a given temperature.

† Also expressed as the weight of water per weight of dry air.

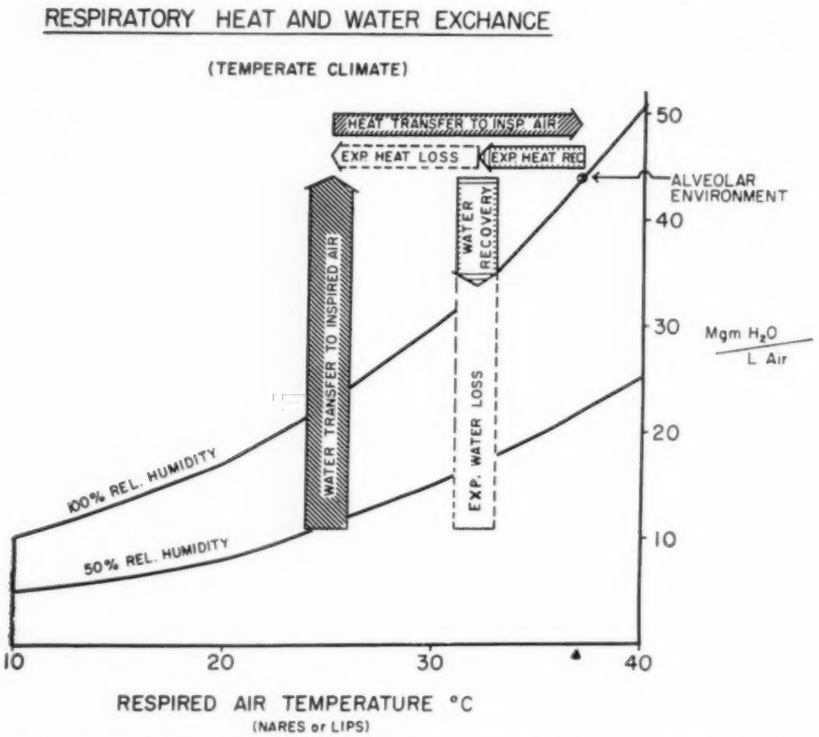


FIG. 3. Respiratory tract heat and water exchange in a temperate environment (25°C., 50 per cent relative humidity). The cross hatched bars, which have been superimposed on Figure 1, represent the amount of heat and water transferred to inspired air and recovered from expired air. The open bars illustrate the amount of heat and water lost in expired air.

liter of air in this climate in order to condition it for the alveolar environment therefore equals 34 mg. Fig 3 illustrates this fact and demonstrates the nge of heat and water occurring between r d air and mucosa during respirations in erate climate. As demonstrated in this fig ter and heat are transferred to inspired a te the alveolar environment of 37°C. and cent relative humidity. The cooling of t ucosa produced by this loss of heat and wa r (evaporation) during inspiration lowers the temperature of alveolar air during expiration to approximately 32°C. [*3,5*]. Approximately 20 to 25 per cent of the heat and water transferred to inspired air is recovered during expiration by this cooling process. Since expired air continues to be saturated at this lower temperature [*3,5,13*], the remaining heat and water is lost in expired air. Under average conditions the adult male at rest loses 250 ml. of water and 350 kcal. of heat in his expired air per day. The fact that 20 per cent of the water in expired air can be recovered by lowering the temperature of saturated air only 5°C. is accounted for by the slope of the saturation curve in the range of body temperature. As illustrated in Figure 1, this amount of cooling would condense much less water at lower temperatures where the slope of the saturation curve is diminished.

It is important to note that the ability of the respiratory tract to recover heat and water is based on the degree to which alveolar air is cooled during expiration. This cooling is produced by the mucosa which itself is cooled during inspiration as it conditions inspired air. A low temperature of inspired air will produce greater convective cooling of the mucosa, while a low humidity will produce greater evaporative cooling of the mucosa. Thus it is the temperature and humidity of the climate which ultimately influences the degree to which heat and water are recovered during expiration.

Cold environment: The respiratory cycle in a cold climate demonstrates the ability of the upper respiratory tract to regulate its heat and water losses. As illustrated by the saturation curve (Fig. 1), the amount of water vapor present in air that is 0°C. or colder is negligible. The amount of water and heat required to condition

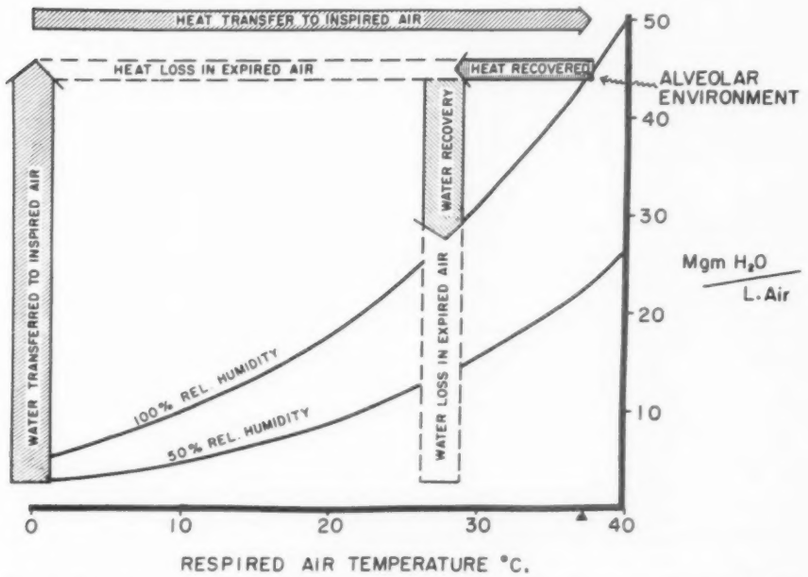


FIG. 4. Respiratory tract heat and water exchange in a cold environment (0°C., 50 per cent relative humidity). The temperature of expired air is lowered to 28°C., resulting in a recovery of 30 to 40 per cent of the heat and water in expired air.

cold air for the alveolar environment is therefore considerable. (Fig. 4.) The increased amount of heat and water lost from the mucosa during inspiration in a cold climate cools the mucosa to a greater extent and alveolar air is therefore made colder when it encounters the upper respiratory tract mucosa during expiration. In a climate of 0°C. and 50 per cent relative humidity, for example (Fig. 4), the temperature of expired air is 28°C. [*18*]. The heat and water recovered from expired air by lowering its temperature to this degree amounts to 30 to 40 per cent of the total given up during inspiration. Despite the fact that the respiratory tract is able to recover a greater percentage of the heat and water transferred to inspired air in cold climates, the total loss of heat and water in expired air is nonetheless greater. (Figs. 3 and 4.) This may account in part for the symptoms of dehydration noted by persons exposed to very cold (and thereby dry) environments for prolonged periods [*19*].

It is noteworthy that the respiratory tract suffers no apparent injury during respiration in very cold climates. This is dramatically illustrated by the case report of a combat flier who was forced to fly with his face exposed to a 250 mile an hour windstream at minus 20°F. for two hours because of destruction of his protective canopy during battle [*1*]. Although he suffered necrosis and sloughing of his facial tissue, the only insult to his respiratory system was a laryngo-tracheitis from which he later recovered. The ability of the respiratory tract to warm exceedingly cold air without itself being injured by freezing is due to the high specific heat of the water that lines the respiratory tract. The specific heat of water equals 1 cal. per gm. (i.e., 1 calorie is required to raise the temperature of 1 ml. of water 1°C.). No other liquid except ammonia has as high a specific heat [*20*]. This physical property of water allows it to store relatively large quantities of heat and therefore act as a depot of heat for the respiratory tract. The specific heat of air, on the other hand, is relatively low, 0.24 cal. per gm. This property of air indicates that its capacity to hold heat is low and therefore the addition or subtraction of relatively small amounts of heat will change its temperature radically.* The water lining the mucosa of the respiratory tract is thus able to protect the mucosa by acting as a heat reservoir. It is the high specific heat of water coupled with the low specific heat of air that enables the respiratory tract to warm very cold air to body temperature without producing thermal injury to the mucosa.

* For example, 500 ml. of air (an average tidal volume) can be warmed from minus 40° to plus 40°C. by the addition of only 20 calories of heat energy. This amount of heat energy can be supplied by 1 ml. of mucosal water lowered 20°C.

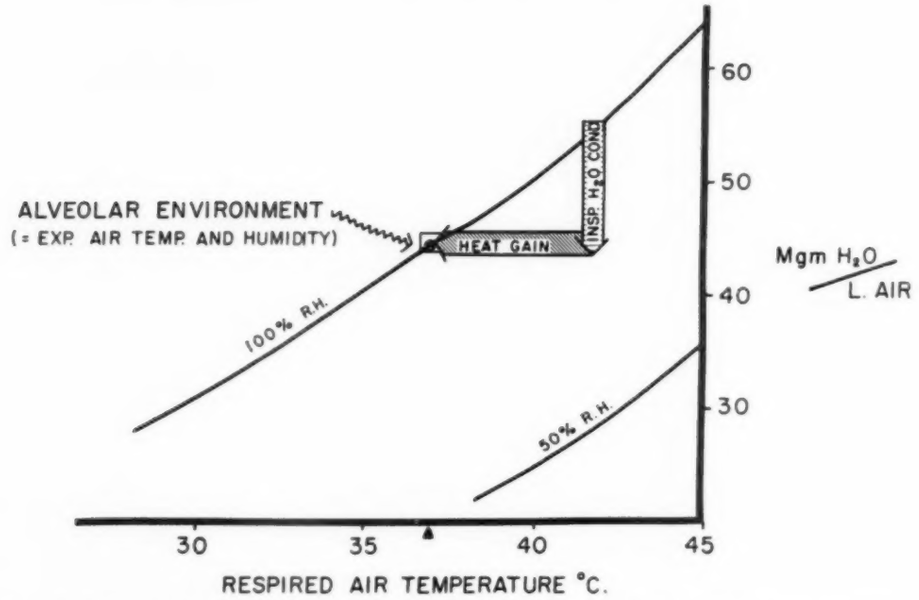


FIG. 5. Theoretical heat and water exchange in a fully saturated high temperature environment (42°C.). On inspiration the respiratory mucosa collects heat by convection and condensation. Under these conditions air is expired from the lungs unaltered and is therefore the same temperature and humidity as the alveolar environment.

Hot environment: In hot climates the respiratory tract is able to increase its heat losses so that body thermoregulation is aided by the elimination of greater amounts of heat. In these climates the humidity of the environment is of particular importance.

If inspired air is both hot and humid no significant evaporative cooling of the upper respiratory tract mucosa occurs during inspiration. In fact if the climate is saturated and above body temperature (Fig. 5) the mucosa may gain heat both from inspired air and from the water vapor in inspired air which condenses on the mucosa to release its latent heat. This heat gain can raise the mucosal temperature to 37°C. or higher. During expiration, therefore, alveolar air is not cooled but is expired fully saturated at 37°C. (Fig. 5.) Under these conditions the respiratory tract is eliminating as much heat as is possible but in net value is gaining both heat and water. These conditions are of course extreme, and would quickly lead to heat stroke. If, on the other hand, the environment is hot but less humid, some evaporation of water from the mucosa will occur during inspiration. (Fig. 6.) This evaporation will cool the mucosa despite the fact that the temperature of inspired air is very high. This occurs because the cooling produced by water evaporation is highly efficient (the latent heat of vaporization of water is 538 cal. per gm.). The fact that evaporative cooling is efficient, coupled with the fact that air having a low specific heat warms the mucosa very little, results in a cooling of the mucosa during inspiration of hot, dry air. Under these conditions the cooler mucosa is able to recover a portion of its water losses during expiration, and the total water loss to the body in a hot climate is diminished. (Fig. 6.) In hot climates, therefore, the humidity of the environment governs the evaporative cooling of the mucosa during inspiration and determines the extent to which the mucosa regains water during expiration.

HEAT AND WATER EXCHANGE IN PULMONARY DISEASE AND CERTAIN RELATED CONDITIONS

The principles of heat and water exchange described have important applications to disease states affecting the respiratory system. The ability of the respiratory tract to condition inspired air and to conserve heat and water during expiration rests primarily on the integrity of the upper respiratory tract mucosa and its normal water content. Any pulmonary disease limiting the ability of the respiratory tract mucosa to exchange heat and water with respired air, or any disease process affecting the temperature of the mucosa will have a definite effect on the ability of the respiratory tract to condition inspired air and to conserve heat and

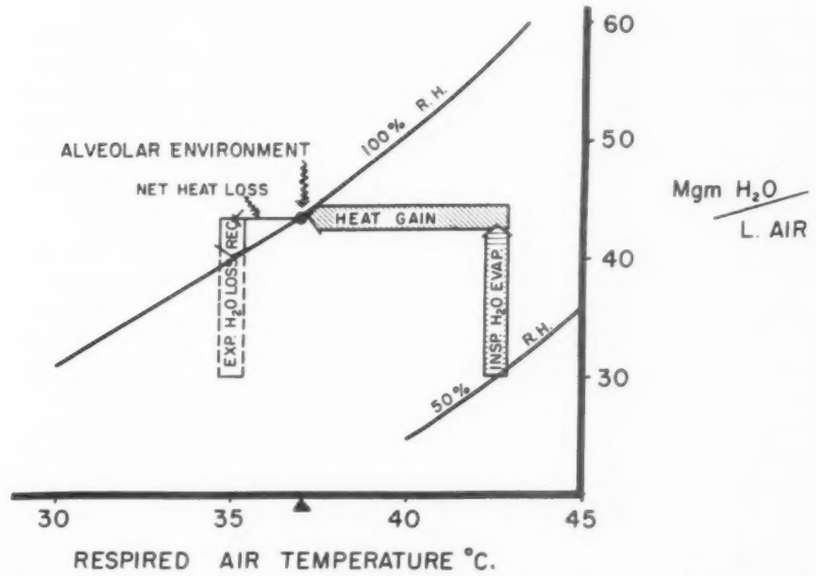


FIG. 6. Heat and water exchange in a high temperature environment (42°C. and 50 per cent relative humidity). Despite the high temperature of the environment, evaporation of water during inspiration cools the mucosa to 35°C. Approximately 10 per cent of this water is recovered by the mucosa during expiration.

water. Excessive loss of water through the respiratory tract leads to an increased viscosity of sputum [*21,22*] and thereby would influence the mucous blanket that supports the normal function of the cilia of the respiratory epithelium. In the discussion that follows the principles of heat and water exchange already outlined are applied to various conditions affecting the respiratory tract. Although the application of these concepts appears logical, the paucity of data regarding actual measurements of respiratory tract temperatures and humidity in disease precludes this discussion from being more than conjectural. Four different clinical conditions that alter the normal processes of heat and water exchange in the upper respiratory tract are discussed briefly.

Fever and Hyperventilation. The temperature of the upper respiratory tract mucosa is determined by the temperature and humidity of inspired air and also by the temperature of the submucosal tissue. Despite the lack of specific temperature measurements, it may be assumed that in febrile states the temperature of the mucosa rises as the body temperature increases. In the presence of fever it may be anticipated that expired air is warmer than usual and that greater amounts of heat and water are eliminated. The elimination of heat by this route aids in the reduction of body temperature in fever; however, the accompanying loss of water accentuates the problem of excessive water loss. Therapeutically, the ideal location for a patient with fever is a cool and dry environment which makes the elimination of heat from the respiratory tract and from the skin more efficient. Water replacement becomes all the more important under these conditions.

Hyperventilation, which frequently accompanies fever, also increases the amount of heat and water eliminated via the respiratory tract. The increased volume of air expired during hyperventilation results in a greater total loss of heat and water. Patients with fever probably use this additional mechanism of hyperventilation to eliminate heat. Subjects with hyperpyrexia due to other causes (climate, exercise) also may increase their heat losses via hyperventilation. Lower animals (dogs, seals) which are unable to perspire through their skin rely heavily on this mechanism to maintain their normal body temperatures. When overheated these animals accelerate respiratory tract losses by breathing rapidly and shallowly (panting). This panting form of respiration permits the exchange of large volumes of dead space air without causing large increases in ventilation of the alveoli, and thus allows the elimination of large volumes of heat and water but minimizes excessive loss of carbon dioxide, thereby preventing the development of respiratory alkalosis [*23*].

Disease of the Respiratory Tract. The apparent increase in the viscosity of bronchial secretions in patients with chronic disease of the respiratory tract suggests that this system suffers an extraordinary water loss in these conditions [*21*]. This deficit can be accounted for in patients having respiratory distress by the increased expiratory water loss associated with dyspnea and/or tachypnea. In patients without respiratory distress, however, it is more difficult to explain. Cole [*15*] has demonstrated that the temperature of normal nasal mucosa increases when patients are given vasodilating drugs. The mucosa of the remainder of the respiratory tract responds in a somewhat similar manner to acute or chronic infection, i.e., submucosal vessels dilate in response to inflammation. Although the temperature of the respiratory tract mucosa has not been measured in disease, it appears reasonable on this basis to assume that the temperature of the mucosa and expired air is increased. The accompanying extra loss of heat and water from the mucosa under this circumstance could lead to a drying of the mucous film covering the respiratory epithelium. The increased viscosity of mucous depresses the normal ciliary action [*22*], and also may reduce the facility with which the respiratory tract in disease exchanges heat and water. Because of this increased viscosity, cough is less effective (less productive) and mucus is further retained.

It appears important, therefore, to prevent dehydration and to humidify the inspired air in patients who have disease of the respiratory tract; particularly if they are dyspneic and/or febrile. If these patients require oxygen therapy, this becomes a difficult task. Oxygen is supplied as a desiccated (dry) gas and even following passage through a humidifier it often remains cool. Despite an efficent humidifier which may saturate the gas, its low temperature limits the amount of water vapor present. (Fig. 1.) During oxygen therapy it is therefore imperative that the gas is warmed during humidification if further dehydration of the respiratory tract is to be prevented.

The alteration in the air-conditioning ability of the respiratory tract in disease is emphasized by the abnormal response of patients to the inhalation of cold air. Patients with chronic bronchitis, emphysema and asthma often complain of cough and occasionally dyspnea when exposed to cold winter weather. Measurements of airflow resistance in these patients have demonstrated the development of marked bronchospasm following inhalation of cold air [*24*]. It may be concluded that the ability of the mucosa to exchange heat and water is limited in disease and that inspired air is thus conditioned less effectively. For this reason cold air may extend further down the abnormal respiratory tract and thereby add to the irritation of an already irritable system.

Tracheostomy. A tracheostomy eliminates a major part of the upper respiratory tract mucosa from the respiratory cycle and therefore curtails the ability of this system to condition inspired air and to conserve heat and water. When the lower airway must provide heat and water to inspired air, the mucous glands and goblet cells appear to become hyperactive, and excessive mucus production frequently ensues [*25*]. One patient with a tracheostomy observed by us, who because of body burns and renal shut down was dependent on his respiratory tract for his water losses, eliminated 4,200 cc. of water in a twenty-four-hour period, as determined by balance studies. The very high temperature (106°C.) and tachypnea in this patient probably contributed to this huge loss. Measurements of the temperature of air expired from tracheostomies have demonstrated the higher temperature and water content of air expired from this site [*25*]. The use of tracheostomy in patients with severe pulmonary disease or patients who are forced to remain in body respirators for long periods often leads to the development of dry crusts about the stoma of the tube. Such crusts can be effectively reduced or prevented by the addition of extra water vapor to the inspired air [*26*]. Because of these observations, it would appear important to avoid dehydration and to supply humidified air to patients with tracheostomies, particularly if they have associated pulmonary disease.

General Anesthesia. The ability of the respiratory tract to eliminate heat and water may be decreased by as much as 75 per cent during surgical anesthesia [*27*]. Although this is not the major cause of hyperpyrexia in anesthetized patients, it becomes an important consideration to the surgeon and anesthesiologist. It has been demonstrated that the temperature of air in the trachea during anesthesia is 39°C. (102°F.) when the "To and Fro" type of anesthesia apparatus is used [*27*]. When the non-rebreathing type of apparatus is employed tracheal air temperatures are only 34°C. (94°F.). The car-

bon dioxide absorbing cannisters, commonly used in "To and Fro" and circuit types of anesthesia apparatus, both saturate inspired air and warm it to as high as 47°C. (117°F.) [*27*]. This is the result of the interaction of carbon dioxide and soda lime which takes place in these cannisters. As noted in the discussion of hot humid environments (Fig. 5), the respiratory tract may gain heat under these conditions. When the temperature and humidity of the operating room is high, the possibility of hyperpyrexia increases for the anesthetized patient. The type of anesthesia apparatus employed in these circumstances becomes most important. This fact has been recognized in recent years and non-rebreathing types of anesthesia apparatus are being used more frequently.

CONCLUDING REMARKS

There is need for more study of this aspect of human physiology, a study that would prove fruitful not only for the physiologist but the clinician as well. The scant attention paid to these problems in the medical literature may be due in part to the technical difficulties encountered in monitoring the rapid changes of temperature and humidity that occur within the respiratory tract. An application of technics described in the past [*3*], and recently modified [*4*], would do much to add to our knowledge of this aspect of pulmonary function.

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Clinicopathologic Conference

Agranulocytosis and Anuria During Phenylbutazone Therapy of Rheumatoid Arthritis

STENOGRAPHIC reports, edited by Lillian Recant, M.D. and W. Stanley Hartroft, M.D., of weekly clinicopathologic conferences held in the Barnes and Wohl Hospitals are published in each issue of the Journal. These conferences are participated in jointly by members of the Departments of Internal Medicine and Pathology of the Washington University School of Medicine and by Junior and Senior medical students.

THE patient, a seventy year old single white housekeeper at the Central Institute of the Deaf, entered Barnes Hospital for the seventh time on March 1, 1960. She died on March 7, 1960.

The patient's first admission to Barnes Hospital was from May 8 to May 27, 1944. On investigation, she was found to have rheumatoid arthritis, chronic maxillary sinusitis and chronic bronchitis. She was treated in the Washington University Clinics with gold, aspirin and physical therapy. In the intervening years she had intermittent exacerbations with involvement of the hands, wrists, shoulders, neck, temporomandibular joints, lumbar spine, knees, ankles and feet. She was found to be anemic and was given a blood transfusion, iron tablets and "shots." At that time, and again seven months prior to her second admission when she was seen at the National Institutes of Health research center in Bethesda, the cause of her anemia could not be established. While there, a three-month course of hydrocortisone was begun; there was an improvement in her sense of well-being and disappearance of acute joint pains, although chronic joint pain and stiffness continued. The discontinuation of hydrocortisone therapy was followed by a severe state of depression and the appearance of low grade fever and night sweats.

She was admitted to Barnes Hospital for the second time on February 25, 1945, because of a "black-out spell" of one day's duration. On the morning of February 21, the patient felt "faint" and subsequently was adjudged to have had a generalized clonic convulsion by a nurse who was present at the time.

There was a past history of a chronic cough productive of mucoid sputum, as well as periods of night sweats and weight loss. In 1944, the results of all bacteriologic studies of the sputum were negative, and a chest roentgenogram was within normal limits.

On physical examination the blood pressure was 105/65 mm. Hg, pulse 100, temperature 38°C. and respirations 20. The patient was an elderly, lethargic white woman, whose skin was pale and of fine texture. There were 2 by 2 cm. firm, movable lymph nodes in both axillae. The heart was enlarged to the anterior axillary line; the sounds were distant. One observer described a grade 2/6 precordial, slightly harsh systolic murmur. A sharp, tender liver edge was palpated 5 cm. below the right costal margin; the spleen, 1 cm. below the left. There were moderately advanced arthritic changes in the hands with fusiform swelling and ulnar deviation of the fingers, as well as moderately advanced deformity of the elbows, knees, wrists, ankles and feet, with tenderness and some limitation of motion. There was some atrophy of the muscles of the extremities as well as edema of the hands and feet.

Laboratory data were as follows: the hemoglobin was 10.1 gm. per cent, packed red blood cell volume 31 per cent, and the white blood cell count was 6,500 per cu. mm. with a normal differential. The urine specific gravity was 1.015; the pH, 7.5. The blood cardiolipin reaction was negative. Five examinations of the stool for occult blood and neutral fat were negative. The result of cephalin-cholesterol flocculation test was 4 plus on two occasions, the thymol

turbidity was 12.7 units (repeat value was 23.5 units), cholesterol 140 and 174 mg. per cent, the prothrombin level was 70 per cent of the normal value. Normal values were reported for the fasting blood sugar, non-protein nitrogen, serum proteins, alkaline phosphatase, serum bilirubin, uric acid and protein-bound iodine. The electrocardiogram and the roentgenographic studies of the chest, gallbladder, and gastrointestinal tract were all interpreted as being within normal limits. A lumbar puncture revealed normal dynamics and cerebrospinal fluid studies. A Congo red test was reported as showing 65 per cent retention of the dye.

The patient's anemia was found to be normochromic, slightly microcytic, and was corrected by the transfusion of 2 units of blood. Following the period of diagnostic evaluation, the patient was treated with prednisone and subsequently showed marked improvement in exercise tolerance and complete lysis of her fever.

In April 1956 the patient noted the onset of "indigestion," which was variably affected by the intake of food, occasionally relieved by self-induced emesis, and unaccompanied by any evidence of blood loss. She was placed on a bland diet and given magnesium trisilicate and aluminum hydroxide gel.

Over the next year, the patient lost weight. By the time of her third admission to Barnes Hospital on July 18, 1957, which was occasioned by an increase in the severity of her joint pains, there had been a 20 pound weight loss. At the time of this admission, her temperature was 38.8°c. and her physical condition was unchanged. The cephalin cholesterol flocculation was 3 plus, thymol turbidity 22 units, cholesterol 226 mg. per cent with the remainder of the studies confirming the previously noted results and revealing no significant infection. An upper gastrointestinal roentgenographic examination was reported as showing an easily reducible hiatus hernia. Following the appearance of a febrile reaction on withdrawal of steroids, the patient was finally placed on a successful regimen of prednisone, chloroquin and salicylates.

Her fourth admission to Barnes Hospital was on July 21, 1958, on the Ophthalmology Service, where she underwent an uneventful, but successful, bilateral intracapsular cataract extractions. She was discharged on August 9, 1958. She continued to be followed up in the arthritis clinic.

The patient was admitted to the hospital for the fifth time on January 8, 1959, because of "stomach trouble" of several month's duration. While receiving both acetylsalicylic acid with buffers and prednisolone daily, she noted increasing stiffness of her joints, as well as an increased frequency of indigestion and a tendency to vomit recently ingested food.

On physical examination the blood pressure was 90/64 mm. Hg, pulse 80, temperature 37.5°c. and respirations 20. The patient was a chronically ill, white woman, with obvious deformities of her joints, although in no acute distress. The anteroposterior diameter of the thorax was increased and the size of the heart was indeterminate. A non-tender liver edge was palpated 8 cm. below the right costal margin; the spleen was not felt. The results of the remainder of the examination were unchanged except for a trace of pedal edema.

The laboratory data revealed a hemoglobin of 11.4 gm. per cent, packed cell volume 37 per cent, red blood cell count 2.73 million per cu. mm., white blood cell count 5,550 per cu. mm. On urinalysis, the specific gravity was 1.002, pH 6.5, trace albumin; examination of the centrifuged sediment revealed 8 to 10 white blood cells per high power field. Urine culture was reported as revealing a moderate growth of white staphylococcus. The serum albumin was 3 gm. per cent, globulin 3 gm. per cent with a normal pattern on serum electrophoresis. There was a 4 plus C-reactive protein determination and the latex agglutination test was reported to be reactive. All blood chemistries, which were previously reported as being normal, remained within the normal range. For the first time, roentgenograms of the chest were interpreted as showing pulmonary emphysema with questionable early bronchiectatic changes. There was a negative skin reaction to intermediate strength P.P.D.

Once again, treatment consisted of general supportive measures and at the time of discharge on January 12, 1959, marked improvement had occurred.

On December 27, 1959, the patient was admitted for the sixth time because of exacerbation of joint pain for three months.

She had been treated with Cohydeltra,® Bufferin® and an ulcer regimen and, except for intermittent periods of "indigestion," had done well until about three months before admission when she noted stiffness of her back

and aching in the region of her shoulders and neck.

Physical examination revealed a blood pressure of 130/60 mm. Hg, pulse 72, temperature 37.4°C. and respirations 20. There was evidence of weight loss and the patient complained of stiffness of her joints. One observer noted a thyroid nodule. The liver was felt 10 cm. below the right costal margin and was slightly tender.

Laboratory data were as follows: hemoglobin was 9.9 gm. per cent, the packed cell volume 32 per cent, white blood cell count 6,900 per cu. mm. with 51 per cent segmented neutrophils, 7 per cent stab forms, 40 per cent lymphocytes and 2 per cent monocytes. The urine specific gravity was 1.010, pH 7.5, 1 plus albumin (1 gm. per L.), with 25 to 30 white blood cells per high power field in the centrifuged specimen. Results of stool examinations on admission for occult blood and neutral fat were negative. The cephalin-cholesterol flocculation was 4 plus, thymol turbidity 18.3 units, alkaline phosphatase 20.1 Bodansky units (repeat value was 26.5 Bodansky units), albumin 2.5 gm. per cent and globulin 3.1 gm. per cent. The prothrombin level was 52 per cent of the normal value, cholesterol 186 mg. per cent. There was 10.7 per cent retention of bromsulphalein dye after forty-five minutes and 11.8 per cent retention of the Congo red dye. Normal values were reported for the fasting blood sugar, blood urea nitrogen, serum bilirubin, protein-bound iodine and serum electrolytes. The results of four tests for the demonstration of lupus erythematosus cells were reported to be negative. There was evidence of full atrioventricular conduction on the electrocardiogram. The basal metabolic rate was found to be plus 11, plus 17 per cent. The Diagnex® blue test was reported to be less than 0.3 mg., although gastric analysis after stimulation with histamine revealed free acid. Roentgenographic examinations of the chest, gastrointestinal tract, gallbladder and skull were interpreted as showing pulmonary emphysema, considerable demineralization of the skeleton, hiatus hernia, gastroesophageal reflux, diverticulum of the second duodenum, evidence of long-standing increased intracranial pressure, hyperostosis and senile osteoporosis.

After admission the patient's temperature rose progressively to a high of 39.5°C. She became afebrile by the end of the third day and remained so during her hospitalization. She had recovered sufficiently by the second week to be started on physiotherapy. Her alkaline phosphatase was 30 Bodansky units. By the end of the second week she had received two blood transfusions and Butazolidin® had been added to her usual regimen. There was some tendency for the accumulation of slight pedal edema and one observer thought that there was some ascites, although no fluid was obtained by paracentesis. Shortly before discharge the cephalin-cholesterol flocculation was 3 plus, thymol turbidity 20.7 units, albumin 2.3 gm. per cent, globulin 3.5 gm. per cent, alkaline phosphatase 36.2 Bodansky units, calcium 10.7 mg. per cent, phosphorus 3.3 mg. per cent (previous value was 4.5 mg. per cent) and white blood cell count 7,100 per cu. mm. A leucine aminopeptidase test was performed at Jewish Hospital and this was reported to be 545 units (upper limit of normal for female patients is 200 units). She was discharged on February 4, 1960, earlier than had been planned, to conduct some personal business.

The patient's chief complaint on this last admission, March 1 to March 7, 1960, was fever for five days' duration. She was unable to give a history, but it was determined that approximately five days prior to admission fever, anorexia, nausea, vomiting and diarrhea had developed. The patient soon became lethargic.

On physical examination the blood pressure was 135/70 mm. Hg, pulse 120, temperature 39.3°C. and respiration 16. The patient was semi-oriented, slow in response, cachetic and unable to give a coherent history. Her throat was red with exudates on both anterior pillars and on the right an area which suggested early membrane formation. The liver edge was 11 cm. below the right costal margin and occupied the epigastrium and the right upper quadrant.

The laboratory data were as follows: the hemoglobin was 10.1 gm. per cent, packed cell volume 35 per cent, white blood cell count 1,300 per cu. mm. and the differential showed 100 per cent lymphocytes. A throat culture was reported as showing only a normal flora. The chest film was non-contributory.

The patient was treated with parenteral fluids, steroids, penicillin and streptomycin. Tachycardia and fever persisted. On March 3, 1960, the white blood cell count was 4,150 per cu. mm. with 76 per cent lymphocytes, 6 per cent monocytes, 10 per cent young monocytes and 8 per cent stimulated monocytes. There was

increased clumping of the red blood cells on peripheral smear. Sternal marrow aspiration was performed and interpreted as showing maturation arrest in the granulocytic series, a decrease in nucleated red blood cells, and an increase in the number of eosinophils, reticulum cells, lymphocytes, plasma cells and phagocytic clasmatocytes. On March 4, 1960, the patient appeared more alert although her blood pressure ranged around 90/50 mm. Hg and her urine output amounted to about 200 cc. as compared with a total of 400 cc. on the previous day. One observer described broad renal failure casts in the urinary sediment.

On March 5, 1960, the patient's white blood cell count was 5,600 per cu. mm. with a differential of 9 per cent segmented neutrophils, 55 per cent stab forms, 2 per cent juvenile neutrophils, 9 per cent myelocytes, 2 per cent eosinophils, 19 per cent lymphocytes and 3 per cent monocytes. The patient became very irritable and a "Moro-like reflex" was elicited when her name was spoken or when she was touched. A lumbar puncture was non-revealing. A morbilliform eruption developed over the trunk. Her blood urea nitrogen was 87 mg. per cent, sodium 145 mEq. per L., potassium 3.9 mEq. per L., CO_2 13.1 mEq. per L., chloride 108 mEq. per L., white blood cell count 26,000 per cu. mm., packed cell volume 37 per cent, hemoglobin 10.4 gm. per cent, with a differential of 42 per cent segmented neutrophils, 41 per cent band forms, 3 per cent myelocytes, 7 per cent metamyelocytes, and 4 per cent lymphocytes. On March 5, 1960, an indwelling catheter was inserted and during the next two days there was complete anuria, as well as total unresponsiveness on the part of the patient. During the last twenty-four hours of the patient's life her blood pressure fluctuated around 70/40 mm. Hg. On the morning of March 7, 1960, she died quietly.

CLINICAL DISCUSSION

DR. EDWARD H. REINHARD: From the descriptions of this patient's physical findings, it would appear that she had rather typical rheumatoid arthritis. It is my understanding that lupus can produce changes in the joints which are at times almost indistinguishable from those of rheumatoid arthritis. I would think, however, that this diagnosis has been fairly well excluded by the innumerable negative reactions to L.E. tests on her multiple admissions. Dr. Hagemann, would you agree that this patient had well-established rheumatoid arthritis?

DR. PAUL HAGEMANN: I have no doubts about it at all.

DR. REINHARD: Over the sixteen-year interval during which she was followed up, the patient received just about every type of treatment that has been advocated for rheumatoid arthritis, including the administration of gold, salicylates, steroids and phenylbutazone. Do you have any comments about this patient's response to therapy?

DR. HAGEMANN: She had persistently active disease, but we were in a sense proud that this seventy year old woman was gainfully employed up until the time of her last admission to the hospital. Therefore, one could consider that some success resulted from her management. She varied in her therapeutic responses from time to time, but symptomatic control was best with small doses of steroids.

DR. REINHARD: One of the interesting features of this patient's long chronic course was the steadily progressive hepatomegaly.

Secondary amyloidosis occurs in association with chronic disease in which there is extensive suppuration, inflammation or tissue destruction and infection. Such diseases include advanced tuberculosis, chronic osteomyelitis, lung abscess, bronchiectasis, chronic pyelonephritis, ulcerative colitis and various malignant tumors, especially renal carcinoma and Hodgkin's disease. Rheumatoid arthritis is a chronic disease characterized by extensive tissue inflammation, and this disease must, indeed, be added to the list. One of the earliest reports of the association of rheumatoid arthritis and secondary amyloidosis was by Baggenstoss and Rosenberg* who reported the association of amyloidosis with rheumatoid arthritis in two of thirty patients, an incidence of 7 per cent. In subsequent reports, the incidence has varied from 15 to 61 per cent. Mr. Clifford Birge, one of our junior medical students has reviewed the literature on this subject. He found 494 case reports of rheumatoid arthritis analyzed for the presence or absence of amyloidosis. Of these, 125 patients had amyloidosis; an incidence of 25 per cent. This is a substantially higher figure than I would have anticipated.

DR. SOL SHERRY: May I ask, Dr. Reinhard,

* BAGGENSTOSS, A. H. and ROSENBERG, E. F. Visceral lesions associated with chronic infectious (rheumatoid) arthritis. *Arch. Path.*, 35: 503, 1943.

whether the 25 per cent incidence of amyloidosis was observed among patients with severe chronic active rheumatoid arthritis, or among all patients in whom a diagnosis of rheumatoid arthritis had been made at one time or another?

DR. REINHARD: Most of these patients had clinically significant, long-standing rheumatoid arthritis. Dr. Sherry, would you comment on the evidence for and against secondary amyloidosis in this case?

DR. SHERRY: It is a very likely possibility. The patient had a long history of chronic active and severe rheumatoid arthritis which was complicated by the development of splenomegaly, hepatomegaly and later by renal manifestations compatible with amyloid infiltration.

DR. REINHARD: Dr. Hagemann, a Congo red test in 1955 was reported as showing 65 per cent retention of the dye in the blood, whereas a repeat test in 1959 showed only 12 per cent retention. These results are widely divergent, and only 12 per cent retention of the dye in the plasma represents a substantially more rapid uptake of the dye by the tissues than average. Is this diagnostic?

DR. HAGEMANN: I do not think so. If 95 per cent were absorbed from the serum by the tissues I would consider that very significant.

DR. WILLIAM H. DAUGHADAY: One factor in the amyloid test that should be mentioned is that Congo red is normally transported in the plasma bound to serum albumin. The 11.8 per cent retention in the plasma, was the result of a test performed at a time when the patient's serum albumin was quite low. This may have been a factor which led to the more rapid disappearance of the dye as compared with the results of the previous test.

DR. REINHARD: Let us consider two other interesting laboratory findings in this case; namely, the alkaline phosphatase and the leucine aminopeptidase results. The alkaline phosphatase varied between 20 and 26 Bodansky units during the last few months of the patient's life, and the leucine aminopeptidase test was reported to show an extremely elevated value of 545 units. Leucine aminopeptidase is a proteolytic enzyme capable of hydrolyzing L-leucine peptides. It is widely distributed in plants, in bacteria and in animals, and has been demonstrated in all human tissues which have been assayed. The level of enzyme is particularly high in the duodenum, the kidney and the liver. The intracellular function of this enzyme is not known, but Rutenburg* believes that it probably involves hydrolysis of a peptide bond near an L-leucine residue or perhaps it involves the transfer of L-leucine from one peptide molecule to another. In the small intestine this enzyme is active in the terminal phases of protein digestion. According to Rutenburg, the enzyme can be readily demonstrated in gastric juice, bile, duodenal secretions, pleural and peritoneal fluids, spinal fluid, and in urine and serum in normal persons. The upper limits of normal for the serum leucine aminopeptidase activity are stated by Rutenburg to be about 200 units for males and 185 units for females. The upper limits of normal for the urinary concentration are 140 units for men and 70 units for women. The serum level of this enzyme has been found to be normal in most malignant diseases, in many metabolic disorders, in a wide variety of degenerative diseases and in a wide variety of clinical infections. Rutenburg measured the serum and urinary enzyme activity in sixteen patients with various lymphomas, leukemias and related disorders. The urine leucine aminopeptidase activity was elevated in all patients in whom it was measured, but the serum activity was 200 units or below in every patient except one man who had a lymphoma invading the head of the pancreas.

In other studies it has been shown that the concentration of this enzyme is increased in pregnancy; normally it drops off shortly after delivery. In extrahepatic obstructive jaundice due to any cause, the level of leucine aminopeptidase is greatly increased. It is increased also in acute hepatitis, in metastatic tumor to the liver and particularly in carcinoma of the head of the pancreas. This is a disease in which the highest levels have been found (450 to 910 units in serum).

Dr. Shatz, articles concerning a bewildering array of new enzyme tests have appeared in the recent medical literature. Would you comment on the significance of the leucine aminopeptidase test first, and then perhaps on some of the other tests?

DR. BURTON SHATZ: In reviewing the literature on this subject and also getting the results from the Jewish Hospital laboratory where they have made roughly about 1,000 determinations, I have sorted out the subjects who showed an elevation of 500 units or more. There were only

* RUTENBURG, A. M., GOLDBARG, J. A. and PINEDA, E. P. Leucine aminopeptidase activity. *New Eng. J. Medicine*, 259: 469, 1958.

six in this group; three had carcinoma of the pancreas, one had carcinoma of the ampulla with marked obstructive jaundice; one had carcinoma of the colon with liver metastases. The highest value, 1,148 units, was obtained in this group, and was in a patient with Thorazine® hepatitis. Most of the investigators who have reported on this subject have concluded that the elevation of the leucine aminopeptidase is a reflection of some interference with the dynamics of the intra- or extrahepatic biliary system. In other words, there must be an obstruction somewhere in the biliary tract. This test is not a specific test for carcinoma of the pancreas. In subjects with carcinoma of the head of the pancreas there is a high incidence of elevated leucine aminopeptidase because of the great frequency of metastatic involvement of the liver causing intrahepatic obstruction, as well as obstruction to the common duct.

DR. REINHARD: If we considered the elevated level of alkaline phosphatase in this patient alone, we would have to consider both obstructive biliary disease and perhaps bone disease. Would the elevated leucine aminopeptodase exclude bone disease as the cause of the high alkaline phosphatase activity?

DR. SHATZ: Leucine aminopeptidase activity certainly has not been reported as being elevated in any of the bone diseases. The fact that both the alkaline phosphatase and leucine aminopeptidase are so elevated would make one think of some primary disease going on in the liver. We know the liver is markedly enlarged and there is marked impairment of liver function. The amazing thing is that there is no jaundice evident in this patient. Perhaps this patient had cirrhosis of the liver as a result of hepatitis from transfusions or the gold therapy and then developed a primary tumor of the liver. This might explain the elevated alkaline phosphatase and leucine aminopeptidase as a result of intrahepatic obstruction.

DR. REINHARD: There have been several other tests of enzyme activity reported in the recent medical literature. One of these is called the 5-nucleotidase test and another is the arginine exopeptidase test.* Dr. Shatz would you care to gaze prophetically into the future and attempt to predict whether or not these new tests are going to really help us significantly?

* NARDI, G. L. Serum "trypsin" (or arginine exopeptidase) screening test for cancer of the pancreas. *Gastroenterology*, 38: 50, 1960.

DR. SHATZ: I think the problem is that none of these enzymes are really specific to any one organ, and since they are so widely distributed in the body it is difficult to make a specific diagnosis on the basis of the determination of any one enzyme.

DR. DAUGHADAY: I would like to make a comment about such an old-fashioned test as the alkaline phosphatase. Actually there is a good deal of confusion about the alkaline phosphatase because different substrates are used for the hydrolysis. In this institution we use the p-nitro-phenylphosphate developed by Dr. Lowry and Dr. Bessey, and we express the results in Bodansky units just by using a correction factor. The high alkaline phosphatase in this institution seems to be much higher than that which is obtained with the standard Bodansky method.

DR. REINHARD: Dr. Karl?

DR. MICHAEL M. KARL: I think one ought to say a word about the use of 5-nucleotidase plasma values because this enzyme determination may have practical application in the future. This enzyme is a specific phosphatase in contrast to the alkaline phosphatases. From the clinical standpoint, this is of interest because when these determinations are carried out in parallel with alkaline phosphatases, they are found to be elevated only when alkaline phosphatase elevations are associated with disease of the hepatobiliary tree or the gastrointestinal tract. They are not elevated when plasma alkaline phosphatase elevation is of bone origin, as for example in Paget's disease.

DR. REINHARD: There was much discussion in this patient's chart concerning the possibility of carcinoma of the head of the pancreas, in view of the leucine aminopeptidase levels. Dr. Lonergan, do you think that we should make this diagnosis, or is there any other reasonable explanation you can think of for these elevated enzyme levels?

DR. WARREN LONERGAN: I think it is difficult to make such a diagnosis, although it is tempting. I had considered, prior to the changes noted in the last year of life, that the patient probably had secondary amyloidosis. However, when she began to have evidence of even more rapid enlargement of the liver, and rising alkaline phosphatase, and when the special serum studies became available, other possibilities occurred to me including carcinoma. I suspect the best possibility is still either a hepatic cirrhosis

TABLE 1
WHITE BLOOD CELL COUNTS ON LAST HOSPITAL ADMISSION

Days After Onset of Fever	White Cells (per cu. mm.)	Cell Types (%)						
		Segmented Neutrophils	Stabs	Juvenile Neutrophils	Myelocytes	Eosinophils	Lymphocytes	Monocytes
5	1,300	...	...	...	...	...	100	...
7	4,150	...	...	...	...	...	76	24
8	3,050	...	...	...	...	1	85	11
9	5,600	9	55	2	9	2	19	3

or a secondary amyloidosis, with a neoplasm superimposed.

DR. REINHARD: I would have expected if this paient had carcinoma of the head of the pancreas sufficient to produce these striking changes, that she would have had jaundice, at least terminally. This patient was never jaundiced. Does this disturb you?

DR. LONERGAN: One is disturbed by that, but I have seen two cases recently with just exactly that feature. There was no jaundice, but the patients had definite pathologic evidence of carcinoma in the head of the pancreas with high alkaline phosphatase; but apparently not enough block of the common duct to produce clinical jaundice.

DR. REINHARD: Dr. Karl, what do you think is the cause of the hepatomegaly?

DR. KARL: I would think that this patient is certainly a good candidate for secondary amyloidosis of the liver. The clinical findings and the laboratory findings are all compatible. Other possible causes of hepatic damage have been mentioned. This patient received gold at one time which can cause jaundice and liver injury. In any chronic debilitating disease, nutritional factors compromise the liver. This patient had been receiving steroids for a long time. It is known that patients receiving steroids may show rather marked fatty changes in the liver. This has also been demonstrated in animals. I am inclined to believe that this patient has amyloidosis of the liver. Ross, Iber and Harvey's report* on the significance of the alkaline phosphatase in infiltrative disease pointed out that in patients with amyloid disease of the liver values may be high. It is not the rule to have a positive reaction to flocculation tests, but they do occur. The relatively small amount of bromsulphalein retention is also compatible with amyloidosis of the liver, as is lowering of the serum albumin and elevation of globulin.

DR. REINHARD: Let us now consider the terminal hematologic problem. You will recall that at the time of the last admission, the patient had had fever for five days, followed shortly by anorexia, nausea, vomiting and diarrhea. The day before admission she became lethargic and partially disoriented. She had been taking phenylbutazone, 100 mg. three times a day, for a period of eight weeks. Examination on admission showed a confused, cachetic, elderly woman. Her throat was very red; there was exudate on the tonsilar pillars, and a marked hepatomegaly. The hemoglobin was 10 gm. per cent; this was about the degree of anemia she had had for many years. The blood counts during the first five days in the hospital are recorded in Table 1. Many of the monocytes on the seventh or eighth days after onset of the fever were immature.

Bone marrow examination was performed on the seventh day after onset of the fever. The bone marrow was very cellular, and showed what could be described as a striking maturation arrest; there were many promyelocytes and some myeloblasts, but almost no granular cells at maturation stages more mature than the promyelocytes. There were numerous monocytes, increased numbers of eosinophils, reticulum cells, plasma cells and a good many lymphocytes. The non-mature granulocytic cells which were present were deficient.

This was considered to be a classic example of agranulocytosis due to drug idiosyncrasy. I would

* ROSS, R. S., IBER, F. L. and HARVEY, A. M. The serum alkaline phosphatase in chronic infiltrative disease of the liver. *Am. J. Med.*, 21: 850, 1956.

like to emphasize that in this disorder, the granular leukocytes may disappear from the blood in a matter of hours and, as occurred in this case, the reappearance of granular cells in the blood may also occur quite dramatically over a period of a day or so. Dr. Brittingham, at various times it has been claimed that eosinophila and monocytosis are favorable prognostic signs in this disease. Do you believe this to be so?

DR. THOMAS E. BRITTINGHAM: I cannot make any comment on the eosinophilia. I would agree with most people that monocytosis, just as it did in this patient, often heralds the return of neutrophils to the peripheral blood.

DR. REINHARD: At one time it was stated that eosinophilia was a favorable prognostic sign, but it is my belief that subsequent studies have not confirmed this. Would you tell us your concept of the mechanism for the striking changes that occur so rapidly in agranulocytosis due to drug idiosyncrasy?

DR. BRITTINGHAM: I believe that the bone marrow has been badly injured by the drug that the patient is taking, and the patient is agranulocytic because his bone marrow is not making neutrophils effectively. In addition to that, infection has usually developed and so has a large peripheral demand for whatever neutrophils that are being made.

DR. REINHARD: Is it correct to say that bone marrow is damaged by the drug, or is the damage due to a hypersensitivity reaction to the drug?

DR. BRITTINGHAM: I have always guessed it was the drug. The morphologic appearance of the bone marrow in agranulocytosis regularly is that of a badly injured bone marrow which is not working well. One can almost invariably infer from simply looking at agranulocytic bone marrow that they are not making white cells satisfactorily. They are sometimes hyperplastic, but as we all know, a hyperplastic bone marrow is not necessarily producing cells rapidly. Now, I said what I did because there is not very much evidence today that antibodies cause severe damage to the bone marrow. We conventionally think of an antibody-mediated hematologic disease as one in which there is rapid peripheral destruction of blood cells, with accompanying very rapid formation of the same cells by the bone marrow. Such a marrow is hyperplastic and shows abundant mature cells. The marrow of drug-induced agranulocytosis *before recovery has begun* usually shows myeloid hyperplasia and almost invariably shows a dramatic paucity of the more mature myeloid elements.

DR. REINHARD: If this is not due to a hypersensitivity antigen-antibody reaction of some kind, how do you explain the fact that a patient can take a given drug for a considerable period of time without any reaction and then suddenly re-administration of the same drug causes profound agranulocytosis?

DR. BRITTINGHAM: I would say that the reason for this is that all of us are chemically unique, unless we happen to have an identical twin, and therefore the response of each one of us to a given drug is probably a little bit different. This, I would think, as Motulsky* has suggested, in terms of genetic susceptibility to drug actions.

DR. REINHARD: Why should a person who shows no toxic reaction to a drug for a long period of time suddenly develop profound toxic marrow changes?

DR. BRITTINGHAM: I think that we will probably find this true more than we think right now, Dr. Reinhard. For example, one may acquire infections as he goes through the week. Also, the accumulated dose of the drug taken changes during the week.

DR. REINHARD: Well, I certainly admire Dr. Brittingham's refusal to go along with the prevailing concepts. On the other hand, Dr. Brittingham, this is not the generally accepted opinion that you are expressing here, is it?

DR. BRITTINGHAM: No, but I think it is becoming a progressively more common opinion aided and abetted by the difficulty people are having in demonstrating typical antibodies in patients such as the one we are discussing.

DR. REINHARD: Dr. Brown, what drugs most commonly produce agranulocytosis?

DR. ELMER BROWN: There is a list of drugs that has been accumulated by the A. M. A. Subcommittee on Blood Dyscrasias that is about twenty or twenty-five pages long, that have been associated with, but not necessarily incriminated in, agranulocytosis or leukopenias. I think that it would be unprofitable to list more than a sampling of them. Some of the common offenders are: chlorpromazine, chloramphenicol, acetophenetidin, reserpine and thiouracil derivatives. The classic one that is always cited is aminopyrine, which during the late 1920's or early 1930's caused quite a few cases of agranulocytosis and fatalities. This drug

* MOTULSKY, A. G. Drug reactions, enzymes and biochemical genetics. *J. A. M. A.*, 165: 835, 1957.

probably works in the same fashion as phenylbutazone. Certainly phenylbutazone is a drug that has been incriminated in many cases, and was the only drug given in some fatal cases of agranulocytosis. In 1953 Leonard summarized the literature on this subject.* He found 1,500 patients who had received phenylbutazone. Of these, approximately .6 per cent showed agranulocytosis. There is a long list of toxic reactions such as edema, nausea, vomiting, jaundice, and so forth, but 3 per cent of all toxic reactions shown were agranulocytosis in this series. The relationship of toxicity to the dose of the drug was quite variable. The total dosage ranged from 5 to 40 gm. The time of onset of agranulocytosis after the drug had been started also was quite variable, from thirteen to sixty days, and the dosage per day varied from 400 to 1,600 mg. So I think that one cannot generalize about phenylbutazone's causation of agranulocytosis since, as Dr. Brittingham has already pointed out, there is individual susceptibility here that is very hard to explain.

DR. REINHARD: Dr. Brittingham, do you think there is any relationship between patients who take a given drug over a long period of time in whom a gradual leukopenia develops, and patients in whom agranulocytosis of sudden and dramatic onset develops? Do you believe that the mechanism of production of the blood and bone marrow changes is the same in these two situations?

DR. BRITTINGHAM: I do not know, Dr. Reinhard. That is a very good question; one to which I, too, would very much like to know the answer.

DR. REINHARD: Dr. Hagemann, you have found phenylbutazone, I believe, very useful in the latest treatment of rheumatoid arthritis; and I take it that you believe that the advantages of this drug are such as to outweigh the occasional occurrence of this unfortunate hematologic reaction. Is this correct? How many times have you seen agranulocytosis due to phenylbutazone in your practice?

DR. HAGEMANN: This is the only time, and I knew it would be presented as a clinicopathologic conference. However, I think this is a very useful drug. We try to keep dosages small, but will use it in conjunction with steroids, because of the potential danger of larger doses of steroid. In several hundred patients receiving 200 to 300 mg. of phenylbutazone a day this is the only time I have seen any leukopenia.

DR. REINHARD: It should be emphasized that although agranulocytosis was a highly fatal disease at one time, now that we have antibiotics and can vigorously treat the infections, the great majority of patients do recover. Therefore, even though this can occur in association with the use of a drug like phenylbutazone, recovery is the rule rather than the exception. This patient recovered dramatically from her agranulocytosis only to die on the day when large numbers of mature granular leukocytes reappeared in the peripheral blood.

Dr. Chaplin, at a time when this patient had almost complete agranulocytosis, marked clumping of the red blood cells was noted on the supervital slide. On a previous admission it had been found that the patient had a slight increase in serum globulin, most of which was due to an increase of gammaglobulin. The suggestion was made that the clumping of the red cells might be due to a dysproteinemia. Certainly, clumping of the red cells is not part of the picture of agranulocytosis. Would you have any other explanation for the clumping of the red cells?

DR. HUGH CHAPLIN, JR.: Is it not correct, Dr. Reinhard, that the patient received a large amount of penicillin during her last admission?

DR. REINHARD: Yes, 6 million units a day.

DR. CHAPLIN: I think this raises the interesting possibility that she is one of those patients who has antibodies to penicillin. The syndrome was first described by Dr. Allyn Ley and his coworkers at Memorial Hospital in New York.* Red cells that are distributed commercially to blood banks to test for blood group antibodies are sometimes dispensed in a penicillin-containing medium. Dr. Ley encountered a patient whose serum did not agglutinate or sensitize red cells that had not been exposed to penicillin, but regularly and strongly agglutinated all cells in the commercial penicillin-containing preparation. He made a study of approximately 400 unselected hospitalized patients, and found an anti-penicillin antibody in 10 per cent of them. Subsequent investigation revealed that all the latter patients had received penicillin. The antibody has been characterized recently as to its position among the gammaglobulins. It seems to occur both as a 19-S and as a 7-S gamma-

* LEONARD, J. C. Toxic effects of phenylbutazone. *Brit. M. J.*, 1: 1311, 1953.

* LEY, A. B., HARRIS, J. P., BRINKLEY, M., LILES, B., JACK, J. and CAHAN, A. Circulating antibody directed against penicillin. *Science*, 127: 1118, 1958.

globulin, and is probably the first definite demonstration of an antibody to an antibiotic. It is interesting that patients with the antibody obtain the same blood levels and apparently enjoy the same antibiotic efficacy as those who lack it. Ley has described one patient whose serum contained the antibody and who was receiving 18 million units of penicillin a day; the patient's red cells clumped on a slide and exhibited a positive reaction to a direct Coombs' test. During a brief period of observation the patient had an appreciable drop in hematocrit, presumably due to hemolysis. Furthermore, studies in which red cells have been incubated with penicillin and then given as an injection to patients with the antibody have shown that these cells are rapidly destroyed in the patient's circulation. However, Ley makes the point that with the usual doses of penicillin the clinical hematologic importance of the antibody is probably very small, if not negligible. I think it is quite possible that in the present instance, clumping of the patient's red cells may have been a manifestation of circulating antibody against penicillin.

DR. REINHARD: This is a tremendously interesting suggestion, one that I had not thought of. Dr. Bricker, I have two questions for you. Perhaps, you can answer them both together. First of all, do you think this patient had amyloid disease of the kidney? And secondly, to what do you attribute the terminal anuria and azotemia?

DR. NEAL BRICKER: I would like to ask a question, Dr. Reinhard. The only blood urea nitrogen determination mentioned in the protocol was obtained on the fifth day of the last hospitalization, and was 85 mg. per cent. Was the blood urea nitrogen level determined on admission?

DR. REINHARD: No, not on this last admission. On a previous admission it had been normal.

DR. BRICKER: With respect to the possibility of renal amyloidosis, I think one has to answer this in light of the patient's over-all clinical picture. There are no confirmatory data which would allow this diagnosis to be made with certainty; and, indeed, we do not even know how much protein she was excreting in her urine. Three months before admission a quantitative assessment of protein excretion was made and the value is given as 1 gm. per L., but no mention is made of the total urine output on that day. I think that she may well have had amyloidosis of the kidneys; but, in view of the reported normal blood urea nitrogen three months before admission, the amyloidosis had not evoked very much in the way of permanent nephron destruction to that point.

DR. REINHARD: I am sorry, I have to make a correction there, Dr. Bricker. The patient's blood urea nitrogen on the first of March 1960, was 12 mg. per cent. That was on the day of admission.

DR. BRICKER: I think that this helps to clarify the picture. It is safe to assume then, that if she did have amyloidosis, it had not resulted in extensive nephron destruction. Therefore, one has to explain the terminal event, which culminated in two days of total anuria, on some other basis. I will not go into the differential possibilities in any detail. Let me say, however, that in a patient who dies in a relatively few days with total anuria, one must consider complete obstruction of the urinary tract, which could incidentally result from papillary necrosis, a marked decrease in the volume and/or pressure of the blood perfusing the kidney, and lesions of the renal parenchyma. Included among the latter would be necrotizing angiitis, acute glomerulonephritis and bilateral cortical necrosis; however, there is little evidence in the urine sediment for any of these intrinsic renal lesions. One other process, acute tubular necrosis, must also be mentioned. Although total anuria is extremely rare in this condition, it may occur in the presence of certain complicating features, one of which is hypotension. This patient had hypotension; it was persistent and severe during the last three days of her life.

Of the various possibilities, I think that two may best serve to explain the terminal renal failure. The first is that it was entirely on a hemodynamic basis, that her filtration pressure was simply so low that she formed essentially no glomerular filtrate, and therefore she sustained progressive accumulation of urea and creatinine. The second is that she did have one of the acute devastating renal lesions mentioned.

DR. REINHARD: Dr. Berg, the last question. Terminally, this patient had a very striking Moro's reflex. She would almost jump out of bed when touched lightly. She had these profound mental changes I have alluded to. The skull roentegenographic findings caused some consternation; I, myself, am willing to attribute them to osteoporosis of the skull bones. Do you think this patient had any primary disease of the central nervous system, or was this all the effect

of the terminal metabolic events in relation to the renal failure?

DR. LEONARD BERG: I think this was all secondary. However, in addition to the roentgenographic findings in the skull there was the fact that she had had a convulsion some few years before, without any other neurologic symptoms. I gather that her spinal fluid pressure was normal during the terminal illness. I do not think we need to be concerned about any primary disease of the central nervous system.

DR. REINHARD: I shall close by making the final diagnosis. The patient had long-standing, chronic rheumatoid arthritis with secondary amyloidosis. Agranulocytosis developed, due presumably to the administration of phenylbutazone, from which she was in the process of recovery at the time of death. We may anticipate that the patient had severe infection related to the agranulocytosis which contributed to her death. She had terminal renal failure, which I would be inclined to attribute to hemodynamic factors alone. I do not think she had any primary disease of the central nervous system. I do not think this patient had a carcinoma of the pancreas.

PATHOLOGIC DISCUSSION

DR. GEORGE SORENSON: The appearance of the body at the time of autopsy was that of a moderately well developed, poorly nourished white woman. She had marked deformities of her fingers and toes related to the long-standing rheumatoid arthritis. The heart weighed 310 gm. and the gross appearance was normal. There was a severe laryngotracheobronchitis with extensive ulceration of the mucosa and pseudomembrane formation. The lungs showed bronchopneumonia which was bilateral but was most severe in the upper lobe of the right lung where there were small abscesses. Proteus morganii was obtained from bacteriologic cultures of the lungs. An acute ulcer was found in the pyloric region of stomach about 1 cm. in diameter. There was also pseudomembranous enterocolitis involving the lower portion of the ileum and most of the colon. The liver was pale brown, firm and weighed 2,600 gm. The lobular pattern on the cut surface of the liver was indistinct and replaced by a fine pale gray mottling. The kidneys each weighed 145 gm. and had finely granular surfaces. The adrenal glands together weighed 7 gm. There was a small remote infarct in the right frontal lobe of the brain and a small recent hemorrhage in the pons.

Microscopic examination of the trachea confirmed the acute tracheitis with ulceration and pseudomembrane formation consisting mainly of fibrin, inflammatory cells and cellular

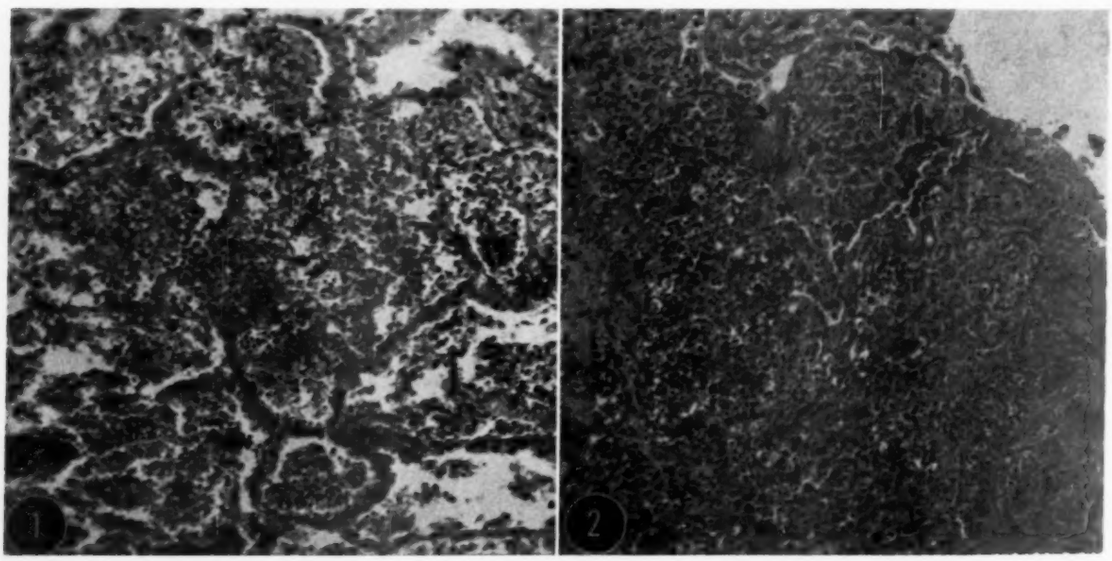


FIG. 1. Acute bronchopneumonia with early abscess formation was found in the lung. Hematoxylin and eosin stain, magnification × 125.

FIG. 2. The mucosal surface of the ileum was necrotic and the epithelium was sloughed. There was an overlying "membrane" composed of fibrin, mucinous material and cellular debris. The submucosa contained many acute inflammatory cells. Hematoxylin and eosin stain, magnification × 125.

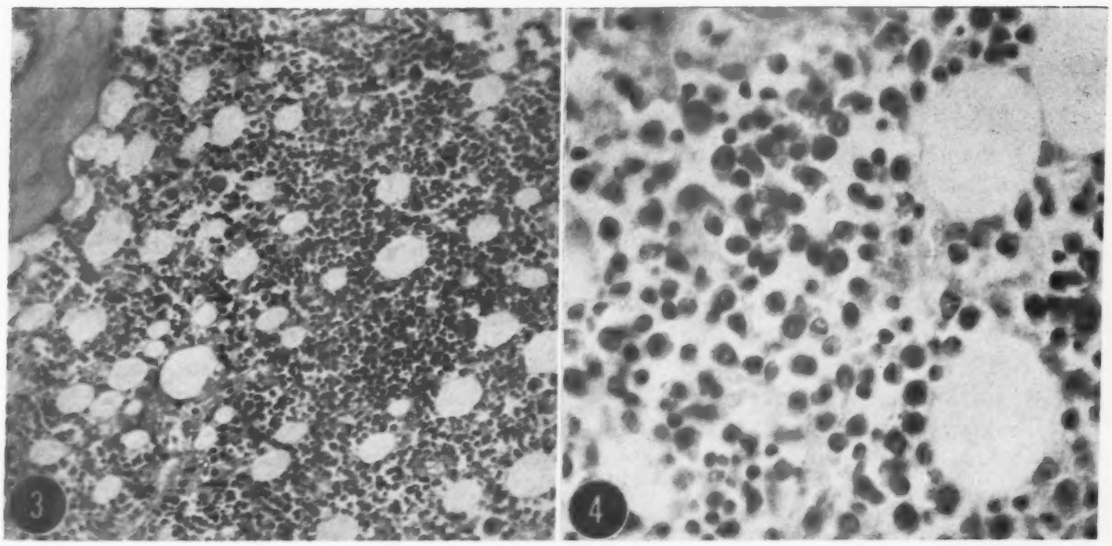


FIG. 3. Moderately hypercellular sternal bone marrow. Hematoxylin and eosin stain, magnification × 125.

FIG. 4. Portion of sternal bone marrow illustrating the prominence of maturing myeloid cells. Hematoxylin and eosin stain, magnification × 450.

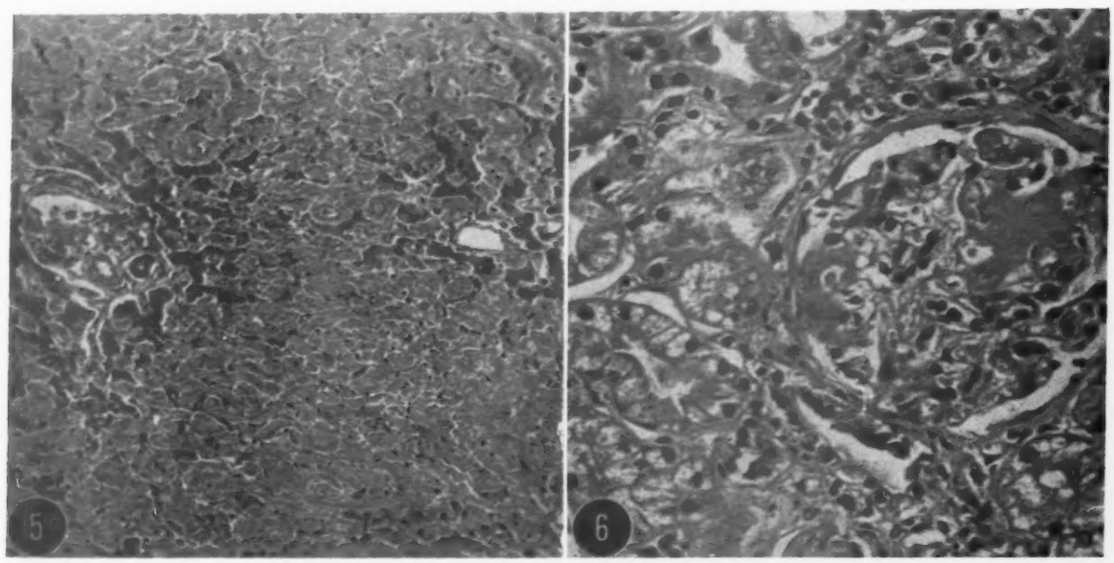


FIG. 5. Severe secondary amyloidosis involving the liver with replacement of most of the hepatic parenchyma. Hematoxylin and eosin stain, magnification × 125.

FIG. 6. Photomicrograph of kidney showing amyloid within a glomerulus and degeneration of the renal tubular epithelium. Hematoxylin and eosin stain, magnification × 250.

debris. Sections of the lungs contained acute bronchopneumonia with abscess formation. (Fig. 1.) The epithelium of the lower ileum and colon was necrotic and there was much superficial ulceration. A membrane of fibrin, mucinous material, exudate and cellulus debris covered the intestinal surface. The submucosa contained many acute inflammatory cells and some vessels contained recent thrombi. (Fig. 2.) The inflammatory response in the intestine was similar to that in the trachea. The remote infarct of the right frontal lobe and the recent hemorrhage in the pons were confirmed microscopically. Sections of the sternal bone marrow were moderately hypercellular. (Figs. 3 and 4.) There was no evidence of a maturation arrest. Marrow from the mid-femur was fatty and showed only a very few hemopoietic cells.

The adrenals revealed marked atrophy of the zona fasiculata which was probably related to the prolonged steroid therapy. The liver contained widespread amyloid deposits which in some places extended completely from the portal to the central zones replacing the liver cells. (Fig. 5.) In other areas there was extensive amyloid between liver cell cords. The nature of the deposits was confirmed by staining with crystal violet.

There was also amyloid within small blood vessels and in the perifollicular areas of the spleen. Amyloid was within glomeruli in a typical pattern and also in the small renal vessels. (Fig. 6.) In addition, there was some degeneration of the renal tubular epithelium.

This patient died as a result of the severe widespread infections which developed following a depression of her bone marrow while she was receiving phenylbutazone therapy. However, at the time of death the bone marrow had recovered and was moderately hyperplastic. It appears likely that the small acute gastric ulcer and the renal tubular degeneration may also be related to therapy with this drug as they have been described previously in patients in whom a toxic reaction developed.* In addition, this patient had severe secondary amyloidosis, particularly in the liver, which may have decreased her ability to counteract these severe complications. The elevations in serum leucine aminopeptidase was probably related to the extensive amyloid deposits within the liver although I know of no precedence for this occurrence.

The primary anatomic diagnoses are as follows: Rheumatoid arthritis affecting fingers and toes; hyperplasia of vertebral bone marrow, moderate; pseudomembranous and ulcerative enterocolitis (gram-positive cocci stained in sections); acute fibrinous peritonitis; pseudomembranous laryngotracheobronchitis; bronchopneumonia with small abscesses; acute ulcer of pyloric portion of stomach; fatty degeneration of renal tubular epithelium; secondary amyloidosis of the liver, advanced; of the spleen, kidneys and adrenals, moderate; of lymph nodes, slight; atrophy of the fasicular zone of the adrenals; arteriolar nephrosclerosis, slight; remote small infarct, right frontal lobe; recent small hemorrhage within pons.

* MAUER, E. F. The toxic effects of phenylbutazone (Butazolidin). *New England J. Med.*, 253: 404, 1955.

Case Reports

The Syndrome of Iodide-Induced Goiter and Myxedema*

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In the past several years a number of reports have appeared incriminating the chronic ingestion of iodide in the production of goiter and myxedema. This paper documents another instance of this phenomenon and reviews the previously accumulated literature on this subject. The data at hand are now sufficient to allow us to describe the clinical manifestations of this syndrome and to suggest a tentative set of criteria for its diagnosis.

CASE REPORT

M. C. (Duke Hospital No. D-35598), a thirty year old unmarried white woman, first came to the attention of the Endocrine Division on the occasion of her seventh admission to Duke Hospital, November 11, 1958. The patient had had severe bronchial asthma since the age of seven years. Since 1953 she had been hospitalized on six previous occasions for control of her pulmonary problems. Therapy had included bronchodilators, sulfisoxazole and antibiotics, postural drainage, breathing exercises, and a prolonged program of desensitization to demonstrated skin allergens and her own nasopharyngeal bacterial flora. For most of the past two years she had received prednisone, 5 to 15 mg. per day; however, this had been discontinued six weeks prior to admission.

Since August 1958 the patient had noted the insidious development of somnolence, periorbital and ankle edema, increasing fatigue, dryness of skin, loss and coarsening of head hair, and an increasing intolerance to cold. During the year prior to admission she had gained 30 pounds. Enlargement of the right lobe of her thyroid had been noted as early as January 1958, but no thyroid function studies were performed at that time. Because of her new symptoms as well as an exacerbation of her asthma the patient was admitted to the inpatient service. Only then was it realized that the patient had been taking a cough mixture containing large quantities of iodides. It was estimated that she had received about 1.3 gm. of iodide daily for the preceding eight months. A review of her Duke Hospital records further revealed that she had been treated with saturated solution of potassium iodide, from 30 drops to as much as 12 cc. daily, almost continuously since 1955.

Although the patient was unaware of any familial incidence of goiter, a sister who visited her was seen by one of us and found to have a large diffuse goiter. Further study of the sister was not possible, and other family members were inaccessible.

Physical examination revealed normal vital signs. Her appearance was characteristically myxedematous, with periorbital edema, dryness of the skin and coarseness of head hair with loss of the lateral portion of the eyebrows. Her voice was hoarse and her reflexes showed marked slowing in the relaxation phase. Her thyroid was diffusely enlarged, with an estimated weight of 50 gm. The remainder of the physical examination was characterized by the stigmata of severe pulmonary emphysema and bronchial asthma.

Routine laboratory studies were essentially within normal limits except for the chest roentgenogram which showed generalized pulmonary emphysema, fibrosis and cyst formation. Pulmonary function studies showed a marked obstructive defect.

The administration of all iodide-containing medications was discontinued two days before her thyroid studies were performed. Due to concurrent asthma the results of the basal metabolic rate determination were not interpretable. A protein-bound iodine (a routine determination by a commercial laboratory) was 14.8 μg. per cent. Butanol extraction was not performed. The serum cholesterol was 362 mg. per cent. Special thyroid function studies carried out at this time are detailed subsequently. Because of intractable asthma the patient was maintained on a

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TABLE I
THYROID FUNCTION STUDIES IN PATIENT M. C.

Parameter	November 1958	March 1959 (4 mo. off iodides)
Clinical status	Hypothyroid	Euthyroid
Body weight (lb.)	150	126
24-Hour I^{131} uptake (%)	1.3	25
Cholesterol (mg. %)	362	267
Protein-bound iodine (μg. %)	14.8	5.2
Basal metabolic rate* (%)	−5	+26
Thyroid iodide space (L.)	8.45	...
Thyroid iodide clearance (cc./min.)	...	25.9†
Estimated thyroid weight (gm.)	50	20
Thiocyanate effect	Discharge	No effect

* Marked respiratory distress during each determination because of basic pulmonary disease.

† Determined in the interval between 0.5 and 1.7 hours after injection of I^{131}.

regimen of prednisone 5 mg. daily and bronchodilators during these as well as all subsequent follow-up studies.

The patient was discharged on the eleventh hospital day without any alteration of her drug regimen except for the deletion of all iodide medications. No thyroid replacement therapy was given. The patient improved rapidly in respect to her endocrine symptomatology. Within four months she had lost 24 pounds, and there were no symptoms suggestive of hypothyroidism.

The patient was readmitted on March 9, 1959, for repeat thyroid function studies. On physical examination she showed none of the features of myxedema previously described. Her thyroid gland was much smaller but was still palpable, with an estimated weight of 20 gm. Her pulmonary status had not improved significantly. Routine thyroid studies showed protein-bound iodine 5.2 μg. per cent, twenty-four hour I^{131} uptake 25 per cent, and serum cholesterol 267 mg. per cent. The determination of the basal metabolic rate was again unsatisfactory due to respiratory difficulties. She was considered to be clinically euthyroid, and as will be detailed, special thyroid function tests were repeated. The patient has remained clinically euthyroid up to her last clinic visit in May 1959, although her thyroid was still palpable at that time.

RADIOIODINE STUDIES

(*Table I, Figs. 1 and 2*)

During the early part of her November 1958 hospitalization, a routine twenty-four-hour radioiodine uptake showed an accumulation of 1.3 per cent of the administered dose. Unknown to us, the patient was still taking the iodide-containing asthma medication during the period of this test. Soon thereafter the history of iodide ingestion was elicited and the incriminated

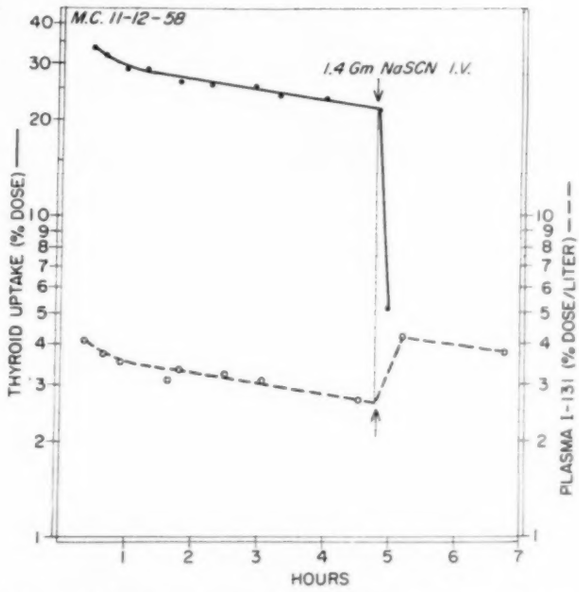


FIG. 1. Character of radioiodine uptake and response to thiocyanate two days after cessation of iodide ingestion.

medication was withdrawn. Two days after cessation of iodide ingestion the patient was given 50 μc. of I^{131} intravenously. Serial determinations of neck uptake and plasma levels were performed, as indicated in Figure 1. Correction was made for residual thyroidal radioactivity from the previous test. A "B" filter was employed to correct for extrathyroidal radiation. The scintillation probe was placed 22 cm. above the patient's thyroid. Plasma samples were measured in a well-type scintillation counter. Counting was performed to an estimated 5 per cent accuracy.

As indicated graphically, a maximal thyroidal accumulation of 34 per cent of the administered dose occurred within thirty minutes. Thereafter there was a gradual fall of thyroidal radioactivity which appeared to parallel the decline in plasma activity. At the end of 4.2 hours 1.8 gm. of sodium thiocyanate was injected intravenously. This led to an immediate discharge of virtually all the accumulated neck radioactivity. At the same time there was a striking rise in the concentration of plasma I^{131}. Thus it may be assumed that practically all the I^{131} in the gland was present as trapped iodide rather than as organically bound iodine. The thyroidal iodide space [*1*], defined as the ratio of iodide in the gland to the simultaneous plasma concentration of iodide, was estimated to be 8.5 L. or approximately seventeen times greater than normal.

In March 1959, four months after the cessation of iodide ingestion, the radioiodine studies were repeated. A routine twenty-four-hour I^{131} uptake study showed an accumulation of 25 per cent of the administered dose. Two days later a repeat tracer test was performed. (Fig. 2.) An intravenous injection of 15 μc. I^{131} was given, and again correction was made for the previous test dose. This time the character of the uptake curve was normal, with a normal thyroidal iodide clearance rate of 26 ml. per minute during the first 2.7 hours. An oral dose of potassium thiocyanate, 2 gm., was given 5.2 hours after the administration of radioiodide. There was no discharge from the gland, indicating that the radioactivity accumulated by the thyroid was not present as inorganic iodide. The significance of the small rise of plasma I^{131} at that time is unclear. It is apparent that the withdrawal of iodide medication resulted in the re-establishment of normal radioiodine dynamics as well as the disappearance of clinical myxedema.

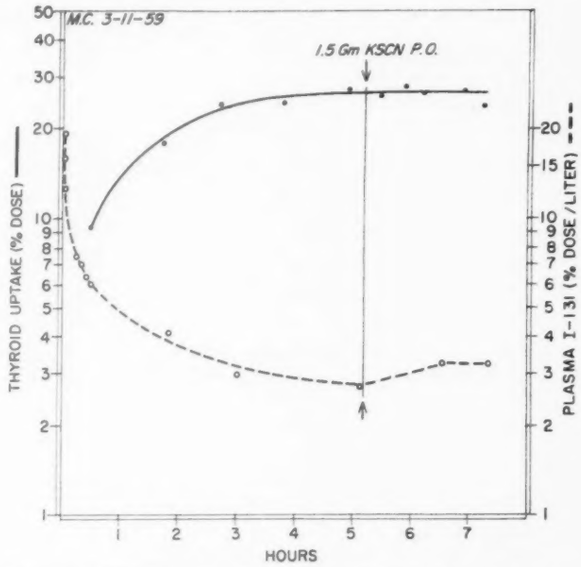


FIG. 2. Character of radioiodine uptake and response to thiocyanate four months after cessation of iodide ingestion.

REVIEW OF THE LITERATURE AND COMMENTS

The previously reported cases of iodide-induced myxedema may be classified according to the presumed status of the thyroid gland prior to the administration of iodide.

Myxedema Developing in Patients with Pre-existing Thyroid Disorders. The earliest reported instances of this syndrome concerned those patients in whom hypothyroidism developed while they were being treated with Lugol's solution for Graves' disease [*2,3*]. It is remarkable that only three such cases are reported in view of the prevalent use of iodides in the treatment of hyperthyroidism prior to the advent of the thiourea compounds.

Three patients with previous subtotal thyroidectomies for Graves' disease are also reported to have had myxedema develop during iodide therapy [*2,4*]. In at least one instance [*2*] the causal relationship between iodide and myxedema appears to have been well established, since hypothyroidism developed on three separate occasions after the administration of Lugol's solution and the symptoms disappeared each time after withdrawal of iodide. However, all patients eventually required thyroid replacement therapy, and it would appear possible that iodides hastened the development of postoperative hypothyroidism.

Myxedema has also been reported to follow iodide treatment of non-toxic goiter. Hurxthal [*5*] described a six year old girl in whom documented myxedema developed following a two-month course of Lugol's solution for a pre-existing goiter. Symptoms of hypothyroidism disappeared within one month after the withdrawal of iodides, and the gland returned to normal size two years later. In the case reported by Bell [*6*] hypothyroidism appeared in a thirty-one year old woman after three years of treatment with Lugol's solution for simple goiter. The patient was given desiccated thyroid for six months, with relief of myxedema. She remained euthyroid for the subsequent four months without any medications.

Myxedema and/or Goiter Developing in Patients Without Apparent Pre-existing Thyroid Disorders. In Table II we have summarized the findings in twenty-three cases previously reported as instances of this syndrome and have added our own case. Unfortunately the diagnostic criteria of the various authors were often inadequate. On clinical grounds a minimum requirement should be the demonstration of regression of goiter and myxedema following the withdrawal of iodides, preferably coupled with return of such signs on reinstitution of therapy. In fourteen of these cases the casual role of iodides was not determined since the patients were given thyroid replacement therapy before any attempt was made to note the effect of simple iodide withdrawal. In two more instances (Cases 11 and 21) only partial improvement followed

TABLE II

MYXEDEMA AND/OR GOITER IN PATIENTS WITHOUT APPARENT PRE-EXISTING THYROID DISORDERS

Author	Case No.	Age (yr.) and Sex	Iodine Preparation *	Time Administered (yr.)	Goiter	Myxedema	Proved by Withdrawal	Kinetic Data † (see text)
Bell 1952 [6]	1	11,F	KI	4/12	+	0	0	0
	2	23,F	KI	4	+	+	0	0
	3	8,F	KI	<1 yr.	+	0	+	0
Raben 1953 [9]	4	42,F	Lipiodol ‡	9/12	+	+	0	+
Morgans, Trotter 1953 [10]	5	66,M	KI	10	?	+	+	+
	6	45,F	NaI	4	+	+	+	+
Goldner et al. 1953 [26]	7	45,F	Varied	30	+	+	+	+
Turner et al. 1956 [27]	8	7.5,M	S.HI	5	+	0	+	0
	9	10,F	S.HI	5	+	0	0	0
	10	5.5,M	S.HI	2.5	+	+	0	0
	11	17,M	S.HI	3	+	0	0	0
	12	8,F	S.HI	3.1	+	+	0	0
	13	5,F	S.HI	2.5	+	0	0	0
	14	7,F	S.HI	2	+	0	0	0
	15	10,F	S.HI	2	+	0	0	0
	16	15,M	S.HI	2	+	+	0	0
	17	9,M	KI	2	+	+	0	0
	18	16,F	KI	4	+	+	0	0
	19	17,M	KI	5	+	+	0	0
	20	11,M	Lugol's	3	+	+	0	0
Hydovitz et al. 1956 [28]	21	52,M	Iodopyrine	12	+	+	0	+
Rubinstein et al. 1957 [25]	22	33,F	KI, iodopyrine	6	+	+	+	+
Paley et al. 1958 [11]	23	60,F	Varied, Lugol's	2	+	+	+	+
Oppenheimer, McPherson 1959	24	32,F	KI, Lugol's	4	+	+	+	+

* S.HI = Syrup of hydriodic acid.

† Kinetic data—includes any timed serial I^{131} thyroid uptake.

‡ Bronchograms one year previously.

iodide withdrawal. On the other hand, in eight cases there was apparently complete recovery after cessation of iodide therapy. In three of the latter iodide was readministered, with recurrence of the syndrome in one instance (Case 6) but not in the other two (Cases 5 and 23) despite nine and eight month courses of iodide therapy, respectively.

In this group it is noteworthy that iodine was generally administered in the inorganic form, primarily for the treatment of pulmonary disorders. In two instances organic iodine compounds were incriminated, iodopyrine in Case 21 and lipidol employed as radiologic contrast material in Case 4. The length of the administration of the iodine preparations before the development of symptoms varied from four months to thirty years, but only in three cases was this period less than one year.

There were eight goitrous patients without myxedema in this group. Only one (Case 5) of the sixteen patients with myxedema did not have a clinically palpable thyroid, but at autopsy this patient had an enlarged gland

which weighed 40 gm. The thyroid gland was studied histologically during the active phase of this syndrome in only three instances: one patient, with goiter but without myxedema (Case 1), showed a colloid storage goiter; two others, with both myxedema and goiter (Cases 12 and 23), showed thyroid hyperplasia with a tendency to colloid depletion.

Certain qualifications must be made in the interpretation of the usual laboratory parameters of thyroid function in this syndrome. As in any other form of myxedema, depression of the basal metabolic rate and elevation of serum cholesterol are useful in substantiating the hypothyroid state. The protein-bound iodine determination, performed in the routine manner, may be elevated because of the precipitation of iodide with plasma proteins [*7,8*]. Determination of butanol-extractable iodine would be a preferable measurement. Interpretation of the radioiodine uptake is of special interest because of the insight it affords into the mechanisms involved. We shall consider this measurement in detail.

In Case 4, reported by Raben in 1953, the suggestion was first made on the basis of serial I^{131} uptake values that the basic defect in this syndrome was a block in organic iodination [*9*]. Twenty per cent of the dose was accumulated in 1.5 hours after administration, but only 7 per cent remained after twenty-four hours. These data were compatible with the hypothesis that the I^{131} in the gland had been present largely as inorganic iodide, since it is known that intrathyroidal iodide is in equilibrium with extrathyroidal iodide, which is rapidly cleared by continued renal excretion. In the same year, Morgans and Trotter [*10*] reported two cases of myxedema which were easily reversed by the withdrawal of iodides. In their first patient (Case 5) these authors originally found a two hour neck:thigh I^{131} ratio of 6.5 (normal, 1 to 10). Significantly, this did not change at the end of twenty-four hours, a finding again consistent with a block in binding. Under normal circumstances, as iodide in the extrathyroidal compartment is transferred to the gland and manufactured into hormone, the neck:thigh ratio rises. Ten days after iodine withdrawal, the two-hour neck:thigh ratio rebounded to 46.3, with a twenty-four-hour uptake of 87 per cent of the administered dose as well as a high protein-bound iodine^{131}. These data suggested that the gland had recovered from the iodide inhibition. Seventy-six days after iodide withdrawal, the two-hour neck:thigh ratio had fallen to 4.4. Essentially similiar results were reported in their second subject (Case 6). These basic observations have since been confirmed by other workers reporting Cases 16, 22 and 23 in the more conventional terms of serial I^{131} uptakes. During iodide ingestion in each of the latter cases the patient showed a rapid initial thyroidal uptake with a relatively low residual value at the end of twenty-four hours, whereas within one to three weeks after cessation of iodide therapy a rebound elevation of twenty-four-hour I^{131} uptake occurred.

Case 23, reported by Paley, Sobel and Yalow [*11*], is of special interest in that detailed kinetic studies were performed. It was shown that the greatly expanded intrathyroidal iodide space remained relatively stable in the face of wide fluctuations of levels of plasma I^{127}. In addition, the authors confirmed the inorganic nature of the accumulated I^{131} by showing that virtually all thyroidal radioactivity could be discharged by thiocyanate. The reinstitution of iodide therapy after the patient had become euthyroid failed to induce goiter or myxedema, although a modest increase in thyroidal iodide space did suggest re-establishment of the iodide effect.

The results in our own case (Case 24) have already been presented and confirm previous observations. The failure to demonstrate a rebound phenomenon in our case probably resulted from the wide spacing of the studies.

Pathogenesis: We shall confine our attention initially only to those cases in which no preexisting thyroid disease was recognized. The demonstration that in this syndrome I^{131} is accumulated as inorganic iodide has been interpreted by most authors as reflecting a block in organic iodination. There is good precedence for such an interpretation in view of the experimental work in rats [*12–14*] and acute observations in man [*15*]. In this regard it is interesting that Galton and Pitt-Rivers [*22*] recently reported that acute iodide loading in rats induced a striking rise in the ratio of intrathyroidal mono-iodotyrosine:di-iodotyrosine, suggesting that iodide blocks the di-iodinating enzyme more completely than the mono-iodinating one. Nevertheless, alternate interpretations of the radioiodine dynamics in patients with this syndrome are possible. As pointed out by Paley, Sobel and Yalow [*11*], only a small fraction of

the expanded thyroidal iodide pool of these subjects would have to be converted into the organic form in order to manufacture a normal quantity of hormone. This fraction would be sufficiently small to escape detection by the experimental procedures employed. It is apparent, however, from the clinical state that the level of circulating hormone is very much depressed. Thus the question arises as to the existence of a block in the normal hormone release mechanism or some disturbance in intrathyroidal metabolism just beyond the stage of organic iodination.

It would appear unlikely that a block in the release of hormone is primarily responsible since one would then anticipate a normal or greater accumulation of intrathyroidal hormone. Colloid depletion was noted in those cases in which biopsy was performed while the patient was myxedematous. Furthermore the observed slow rise in protein-bound iodine and the elevated protein-bound iodine^{131} after iodide withdrawal are consonant with a diminished thyroid hormone reserve [*10,11*]. More directly, Greer and DeGroot [*16*] have shown that iodide did not slow the release of thyroid hormone in a euthyroid patient who had had two prior episodes of iodide-induced myxedema. On the other hand the data of Goldsmith, Herbert and Lutsch [*19*], demonstrating that iodides do inhibit the release of thyroid hormone in patients with Graves' disease, indicate the complexity of the problem and the possibility that more than one mechanism may be at fault. The loci of action of iodides in a larger clinical and physiologic perspective have been discussed by a number of investigators [*17–21*].

According to modern concepts of thyroid physiology it is probable that pituitary secretion of thyroid-stimulating hormone (TSH) increases as the level of circulating thyroid hormone falls in these patients. The development of goiter and the enhancement of the thyroidal iodide space are consonant with this concept, although plasma TSH assays have not been reported thus far. It seems possible that patients with goiter but without overt myxedema have sufficient amounts of circulating thyroid hormone to meet the metabolic requirements of the body but insufficient levels to prevent the increased TSH production by the pituitary. It has been demonstrated by Raben [*23*] in the rat that TSH increases the sensitivity of the thyroid to the blocking action of iodide by increasing the thyroidal concentration of iodide. Thus as increasing amounts of endogenous TSH are released, the thyroid becomes increasingly sensitive to iodide and eventually frank myxedema supervenes. That goiter appears to precede myxedema is illustrated by Cases 1, 22 and 24. One might predict that patients with goiter alone would eventually become hypothyroid with continued iodide ingestion.

The question of why this syndrome appears to be relatively rare among the large population of subjects maintained on iodides remains unsolved. In the rat the thyroid manages to escape from the inhibitory actions of iodides [*22,24*]; whether a similar mechanism exists in man has not been determined. Rubinstein and Oliner [*25*] have suggested that the relative rarity of this syndrome is due to the fact that most patients administered iodides do not take their medication over a sufficiently long period of time and with sufficient regularity to produce myxedema. This concept is borne out by the long histories of iodide ingestion in most patients and by the fact that the symptoms promptly vanished after the responsible medications were stopped. However, it is of interest that in Cases 5 and 22 the full blown picture of myxedema and goiter could not be reproduced by the reinstitution of iodide therapy for periods as long as nine and eight months, respectively.

The possibility that some of these patients had antecedent but inapparent defects in intrathyroidal metabolism which would make them more vulnerable to the effects of iodide should also be considered. In Cases 11 and 21 there was only partial correction of symptoms following the withdrawal of iodides, and the persistent abnormalities in the character of the I^{131} uptake in these two instances also lends credence to this possibility. In both cases (Cases 23 and 24) there remained a minimal degree of thyroid enlargement as long as six months after the withdrawal of iodides. Furthermore, the discovery that our patient had a sister with an impressively large non-toxic goiter unrelated to iodide ingestion must raise the question of a heredofamilial factor in the genesis of this syndome.

These postulated basic mechanisms would be equally applicable to those patients with definite pre-existing thyroid disease. Thus it is conceivable that the group with prior thyroidectomy and those with simple goiter may again have been producing only marginal quantities of

hormone before iodide therapy. The production of myxedema in the few patients being treated for Graves' disease must be considered an unusual variation of the well established effect of iodides in this disorder.

Diagnostic criteria: In the course of clinical practice it may become necessary to decide whether a given case of myxedema is causally related to iodide ingestion. At present, the only certain proof of this relationship consists of improvement following withdrawal of iodides. In the usual case improvement should occur within one or two months.

However, there are certain characteristic clinical features which can heighten the index of diagnostic suspicion. These features are: (1) a prolonged history of iodide ingestion (greater than four months), (2) the presence of a goiter, and (3) certain characteristic alterations in I^{131} kinetics. The latter include (a) a rapid thyroidal uptake in the first few hours after the administration of the tracer dose, followed by a decline to low residual values at twenty-four hours, (b) an enlarged thyroidal iodide space, (c) the dischargability of the accumulated thyroidal I^{131} with thiocyanate, and (d) a rebound phenomenon following the withdrawal of iodide, characeterized by high twenty-four–hour thyroidal uptake together with elevated levels of protein-bound iodine^{131}.

SUMMARY

A case of iodide-induced goiter and myxedema is presented. Radioiodine studies in this patient demonstrated a rapid thyroidal accumulation of tracer which could be discharged by thiocyanate. An increased thyroid-plasma gradient, as reflected by an enlarged thyroidal iodide space, was also demonstrated.

Thirty-two published case reports of presumed iodide-induced myxedema and goiter are reviewed. The cases are classified according to the thyroidal status prior to the onset of iodine ingestion.

The theoretic basis of this syndrome is discussed. It is concluded that the development of goiter and myxedema depends either upon the length and regularity of iodide ingestion or upon a basic sensitivity to iodides, possibly related to some pre-existent subtle defect in intrathyroidal metabolism.

The clinical and laboratory criteria for the diagnosis of this syndrome are tentatively defined.

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Hereditary Multiple Exostoses, Pseudo-Pseudohypoparathyroidism and Other Genetic Defects of Bone, Calcium and Phosphorus Metabolism*

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SINCE the description in 1952 by Albright, Forbes and Henneman [*1*] of the syndrome pseudo-pseudohypoparathyroidism, serious question has been raised as to whether or not it should be classified as a separate and distinct disorder. The similarity and possible relationship of pseudo-pseudohypoparathyroidism to other disorders was acknowledged in the original description. It was believed that the abnormalities were genetically determined, perhaps independently of each other by different genes and that, therefore, one or more features could be present without the others. Consequently, the diagnostic criteria have not been exacting and there has been no clear-cut definition of pseudo-pseudohypoparathyroidism.

In the original report [*1*], pseudo-pseudohypoparathyroidism was compared with pseudohypoparathyroidism, idiopathic hypoparathyroidism and myostitis ossificans progressiva. Since then other disorders have been observed to have some of the features characteristic of this group. Among these have been familial brachydactyly, familial calcification of the basal ganglia, and Turner's syndrome. To this group we should like to add multiple epiphyseal dysplasia and hereditary multiple exostoses. We shall report observations made on four generations of a family, twelve members, who manifested the characteristic features of hereditary multiple exostoses (Fig. 1), and show how some members of the family might well have been classified as either pseudo-pseudohypoparathyroidism or as hereditary multiple exostoses.

In addition, it appeared desirable to review and compare the reported cases of pseudo-pseudohypoparathyroidism, and to describe briefly the several syndromes which are related to, or have been likened to it. Our intention in so doing is to show that pseudo-pseudohypoparathyroidism is not a distinct entity, and that it,

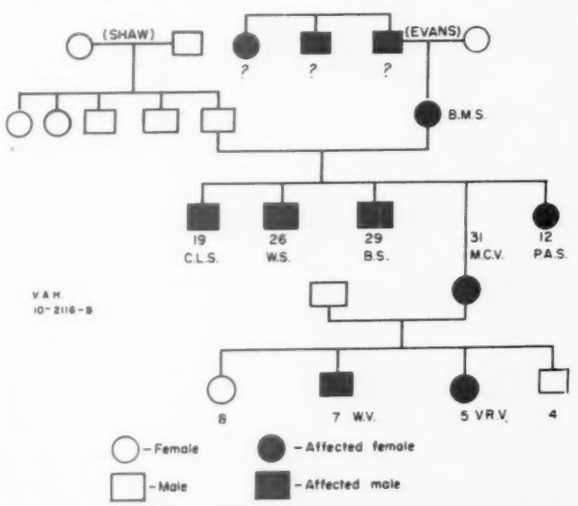


FIG. 1. Pedigree of the S. family with hereditary multiple exostoses.

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along with the other syndromes mentioned, may well be classified together in a broad spectrum of interrelated genetic disorders of calcium and phosphorus metabolism and bone formation.

MATERIALS AND METHODS

C. L. S. (Case II) was studied on the medical ward of the University Hospital, Birmingham, Alabama. Other members of the family were interviewed and examined in the Conecuh County Hospital, Evergreen, Alabama where roentgenograms were taken and blood samples drawn. Blood samples were immediately centrifuged, the serum was separated, kept cold and returned to Birmingham where the serum levels of calcium, phosphorus, creatinine and total protein were determined in both the University Hospital Laboratory and in the Pediatric and Pharmacology Laboratory of the University of Alabama Medical Center.

The Ellsworth-Howard [*2*], phosphate clearance [*3*] and tubular reabsorption of phosphate (TRP) tests [*4*] were performed in Case II and a normal subject between the hours of 10:00 A.M. and 4:00 P.M., with the patients in a fasting state. Hourly urine samples were collected, and analyzed for their phosphorus and creatinine content. At 1:00 P.M., 200 units of parathormone* were injected intravenously. In the middle of the three hour period, before and after the injection of parathormone, a blood specimen was collected and analyzed for phosphorus and creatinine content. The per cent tubular reabsorption of phosphate was estimated, using the following formula:

$$\text{TRP}\% = 100 \times \frac{\text{Phosphate mg.}\% \text{ (urine)} \times \text{Creatinine mg.}\% \text{ (serum)}}{\text{Phosphate mg.}\% \text{ (serum)} \times \text{Creatinine mg.}\% \text{ (urine)}}$$

The hourly phosphorus excretion before and after injection of the same lot of parathyroid extract to these subjects is illustrated in Figure 2. On the day prior to the test, the same procedure was followed, except that the parathormone was omitted. This procedure is suggested by Dent [*5*] and McNeely et al. [*6*] to compare the test results with the diurnal variation of phosphorus excretion [*7*]. It has been suggested that the diurnal variation may mimic the response to parathyroid extract [*8*]. The tubular reabsorption of phosphate in the normal subject was 89.9 per cent before and 84.5 per cent after the administration of parathormone. The values in Case II were 92.4 per cent before and 85.9 per cent after the administration of parathormone. The drop in the TRP was approximately equal in both subjects and the values after the administration of parathormone were in the hyperparathyroid range. The renal clearance of phosphate in the normal subject was 18.7 cc. per minute before and 33.4 after parathormone was given. The values in the patient were 9.7 cc. per minute before and 16.3 after parathormone was given. Thus the administration of parathormone approximately doubled the clearance of phosphate, a normal response [*3*].

* We are grateful to Dr. Glenn Irwin of the Eli Lilly Company and to Dr. H. E. Carnes of Parke, Davis Company for the generous supply of parathormone used in these studies.

OBSERVATIONS

Twelve members of the family shown in Figure 1, including the entire last two generations and two members, B. M. S. and her husband, of the second generation, were examined by the authors. Eight of these subjects had classic hereditary multiple exostoses. Three other members in the first generation of the family pedigree illustrated in Figure 1 were not examined, but were reported by other members of the family to have a similar disorder. All of the affected subjects had multiple bony exostoses, while none that were examined had cataracts, blue scleras, tremors, or a history of seizures. Two of the patients (Case I and Case II), were short-statured, round-faced, and had shortened metacarpals. Two other patients (Case VI and Case VII), in addition to the bony exostoses, also had shortened metacarpals, but were without other abnormalities. The serum chemical findings and response to parathyroid extract (Fig. 2) were normal in all patients studied.

CASE HISTORIES

CASE I. B. M. S., (Fig. 3), the forty-eight year old mother of Cases II, III, IV, V and VI, had been aware of exostoses all of her life. These had ceased to appear and grow after childhood. Except for occasional attacks of asthma for the past fifteen years her medical history revealed no abnormalities. The physical examination was within normal limits except for the patient's short stature, round face, short stubby hands, and numerous bony exostoses. Her blood pressure was 170/108 mm. Hg, height 61 inches, and weight 178 pounds. Roentgenograms of the long bones and hands revealed numerous bony exostoses and a shortened fifth metacarpal on the left. The serum calcium level was 10.4 mg. per 100 ml., phosphorus 2.9 mg. per 100 ml., total protein 7.5 gm. per 100 ml. alkaline phosphatase 3.9 Bodansky units and creatinine 0.7 mg. per 100 ml.

CASE II. C. L. S., (Fig. 4), the eighteen year old son of Case I, was admitted to the hospital for evalua-

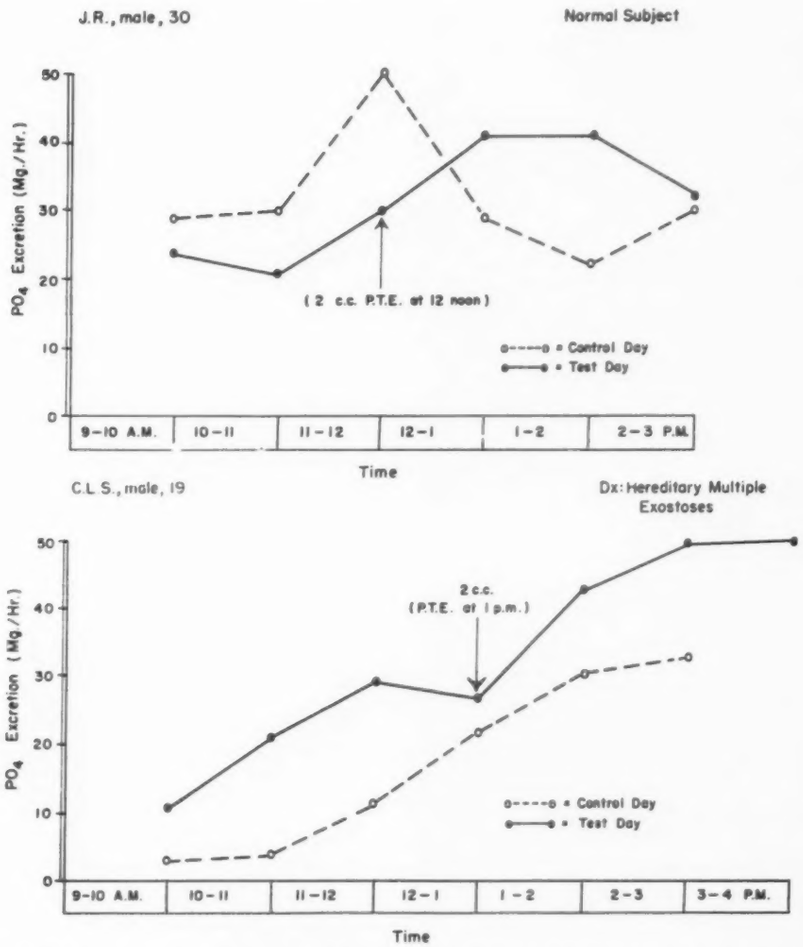


FIG. 2. The response to parathyroid extract administered intravenously to a normal subject and to one subject (C. L. S.) with multiple exostoses. The phosphate excretion at the same time on a control day is also shown.

tion of a heart murmur which had been discovered by his private physician. His only complaint was slight dyspnea on exertion and inability to compete physically with other boys of the same age. He had been aware of multiple exostoses all of his life, but otherwise his history revealed no abnormalities. He was 65 inches in height, and weighed 136 pounds. His blood pressure was 128/88 mm. Hg, and the pulse rate was 88 and regular. The face was round and the neck short and thick. There was no evidence of cataracts; the scleras were not blue. The thyroid was normal in size and consistency. Examination of the heart revealed the point of maximum impulse to be well localized in the fifth intercostal space 2 cm. outside the mid-clavicular line. A prominent systolic thrill was felt over the entire precordium and a grade 2 to 3 harsh systolic murmur was heard in the same area, but was loudest at the apex. The rhythm was normal except for an occasional premature ventricular contraction. The abdominal examination revealed no abnormalities. The genitalia were normal, as was the results of the rectal examination. He had numerous exostoses of the arms and legs, and short stubby hands. The neurologic examination was within normal limits.

The hematocrit was 42 per cent and the white blood cell count 8,500 per cu. mm. with a differential of 69 polymorphonuclear leukocytes, 23 lymphocytes, 6 monocytes and 2 eosinophils. The blood urea nitrogen level was 8 mg. per 100 ml., serum sodium level 142 mEq. per L., potassium 4.4 mEq. per L., chloride 109 mEq. per L., and carbon dioxide 30 mEq. per L. The serum alkaline phosphatase level was 2.2 Bessey-Lowry units, the serum creatinine level 1.6 mg. per 100 ml., and serum protein-bound iodine level 5.5 μg. per 100 ml. Serum calcium determinations on several occasions were as follows: 10.9, 11.2, 9.5, 10.7 mg. per 100 ml. Serum phosphorus levels at the same time were 4, 2.4, 3.6, 3.7 mg. per 100 ml. Roentgenograms of the chest and the abdomen revealed no abnormalities. A roentgenographic examination of the bones revealed numerous exostoses of the upper and lower



FIG. 3. Case I, B. M. S.

extremities and shortened second, third and fourth metacarpals bilaterally, the latter resulting in short stubby hands. The electrocardiogram was normal. Psychologic studies and intelligence quotient tests showed the patient's performance and mentality to be high average. Cardiac catheterization studies revealed an intraventricular septal defect which, it was advised, should not be operated upon at that time. Results of the Ellsworth-Howard test on a control day and on a test day are shown in Figure 2 and compared with the same test made under identical conditions on a normal subject.

CASE III. B. S., the twenty-nine year old brother of Case II, reported the presence of exostoses for as long as he could remember. There had been no increase in the size of the exostoses and no new exostoses had appeared for at least ten years. There was a history of pneumonia at ten years of age followed by empyema, and a history of pneumonia "five or six times" subsequently, the last time about eighteen months prior to this examination. The physical examination and roentgenograms revealed numerous severe bone deformities and exostoses of both the upper and lower extremities. (Fig. 5.) There were no other abnormalities on physical examination except

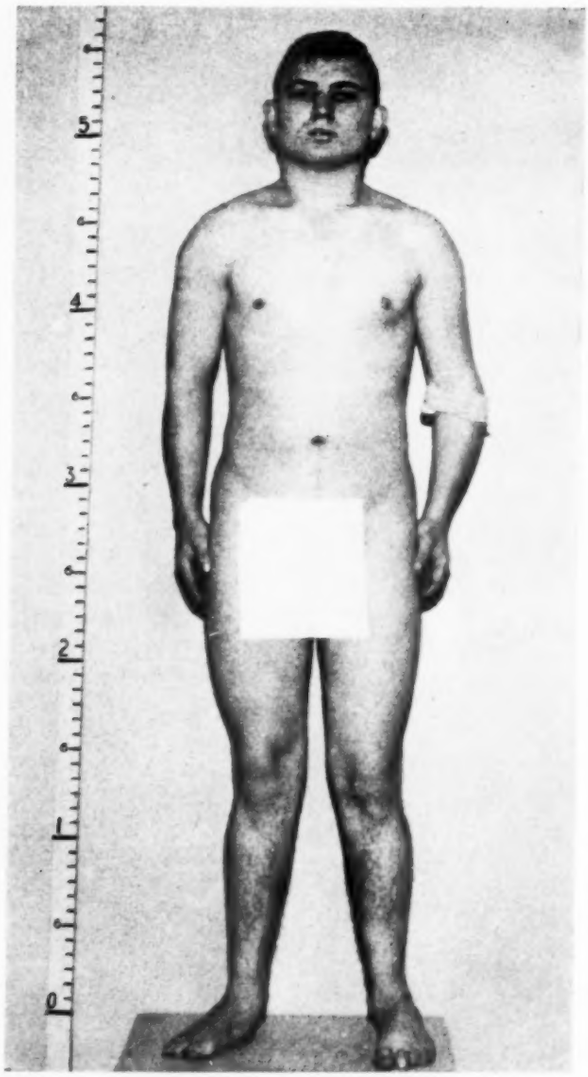


FIG. 4. Case II, C. L. S.

for varicose veins of both legs. The blood pressure was 132/78 mm. Hg, height 67½ inches and weight 136 pounds. The serum calcium level was 9.6 mg. per 100 ml., phosphorus 3.4 mg. per 100 ml., total protein 7.8 gm. per 100 ml., alkaline phosphatase 2.2 Bodansky units and creatinine 0.65 mg. per 100 ml.

CASE IV. W. S., the twenty-six year old brother of Case II, also had exostoses all of his life, with no worsening or new exostoses in the past several years. He had no unusual symptoms or illnesses. Physical examination revealed exostoses, which were confirmed by roentgenographic examination, to be the only abnormal finding. The blood pressure was 140/88 mm. Hg, height 68 inches, and weight 149 pounds. The serum calcium level was 9.9 mg. per 100 ml., phosphorus 3.3 mg. per 100 ml., alkaline phosphatase 1.9 Bodansky units, total protein 7.3 gm. per 100 ml., and creatinine 0.6 mg. per 100 ml.



FIG. 5. Roentgenograms of the arms, wrists and hands of B. S. (Case III).

CASE V. P. A. S., the twelve year old daughter of Case I, had a history that was non-contributory. Physical examination was within normal limits except for exostoses of the upper and lower extremities. The blood pressure was 108/50 mm. Hg, height 59 inches and weight 87 pounds. The serum calcium level was 9.8 mg. per 100 ml., phosphorus 4 mg. per 100 ml., total protein 7.1 gm. per 100 ml., alkaline phosphatase 5.6 Bodansky units and creatinine 0.45 mg. per 100 ml.

CASE VI. M. C. V., the thirty-one year old daughter of Case I and mother of Cases VII and VIII, had had no abnormal symptoms or illnesses. Her blood pressure was 115/70 mm. Hg, height 65 inches, and weight 115 pounds. She had multiple exostoses involving the upper and lower extremities. Roentgenographic examination of the hands and wrists (Fig. 6) revealed bony exostoses and deformities, and a shortened fifth metacarpal on the right. The serum calcium level was 10.4 mg. per 100 ml., phosphorus 2.5 mg. per 100 ml., total protein 7.5 gm. per 100 ml., alkaline phosphatase 1.8 Bodansky units and creatinine 0.7 mg. per 100 ml.

Case VII. W. V., the seven year old son of Case VI, had a history that was non-contributory. Physical examination was within normal limits except for exostoses. The blood pressure was 104/54 mm. Hg, height 48 inches, and weight 51 pounds. Roentgenographic examination revealed exostoses and deformities of the upper and lower extremities, and a shortened second metacarpal on the left which was obvious upon making a fist. (Fig. 7.) The serum calcium level was 10.3 mg. per 100 ml., phosphorus 4.5 mg. per 100 ml., total protein 6.1 gm. per 100 ml., alkaline phosphatase 5.9 Bodansky units and creatinine 0.2 mg. per 100 ml.



FIG. 6. Roentgenograms of the wrists and hands of M. C. V. (Case VI). Note the shortened fifth metacarpal on the right hand.

CASE VIII. V. R. V., the five year old daughter of Case VI, had a history that was non-contributory. Physical examination was within normal limits except for a few exostoses of the upper and lower extremities, confirmed by roentgenographic examination. Her height was 46 inches and weight 45½ pounds.



FIG. 7. Roentgenograms of the wrists and hands, and photographs of the fists of M. V. (Case VII). Note the shortened second metacarpal on the left hand which is apparent both in the x-rays and fists.

TABLE 1

INTERRELATIONSHIP OF VARIOUS GENETIC DEFECTS IN BONE, CALCIUM AND PHOSPHORUS METABOLISM

Syndrome	Idiopathic Hypoparathyroidism	Pseudo-Hypoparathyroidism	Pseudo-Pseudohypoparathyroidism	Myositis Ossificans Progressiva	Hereditary Multiple Exostoses	Multiple Epiphyseal Dysplasia	Familial Brachydactyly	Familial Calcification of Basal Ganglia
Short stature	−	+	+	−	+	+	+	−
Ectopic calcification or ossification	−	+	+	+	−	−	−	−
Metacarpal shortening	−	+	+	+	+	+	+	−
Metatarsal shortening	−	+	+	+	+	+	+	−
Other phalangeal shortening	−	+	±	+	−	+	−	−
Exostoses	−	±*	±	+	+	−	+	−
Basal ganglial calcification	+	+	−	−	−	−	−	+
Multiple congenital defects	+	+	+	+	+	+	+	−

* + = three of first twenty-eight patients.

COMMENTS

In order to compare hereditary multiple exostoses to pseudo-pseudohypoparathyroidism and to interrelate the other syndromes which have one or more similar findings, an understanding of all of these disorders is necessary. These interrelationships are illustrated in Table 1, and a brief summary of each disorder will be presented.

Idiopathic hypoparathyroidism is a rare disorder which may be diagnosed when the following criteria are met [*8,9*]: (1) a low serum calcium level; (2) a high serum phosphorus level; (3) absence of roentgenologic evidence of rickets and osteomalacia; (4) chronic tetany; (5) absence of renal insufficiency, steatorrhea, chronic diarrhea, alkalosis, or a history of thyroid surgery; and (6) phosphate diuresis following the intravenous administration of a potent parathyroid extract. Persons with this disorder usually have signs and symptoms related to hypocalcemia; they frequently manifest other unexplained findings such as cataracts, ectodermal changes of various kinds and mental deficiency [*8,9*].

Pseudohypoparathyroidism is a disorder characterized by the first five diagnostic criteria of idiopathic hypoparathyroidism. It was differentiated from idiopathic hypoparathyroidism by Albright [*10*] because, in certain patients, parenterally administered parathyroid extract did not produce a phosphate diuretic response or clinical improvement following prolonged intramuscular administration. In the original report and in a subsequent report by Albright's group [*11*] other distinguishing features of pseudohypoparathyroidism were emphasized. These included: (1) a body habitus characterized by a short, thickset figure and a round face; (2) short fingers and toes due to shortened metacarpal or shortened metatarsal bones; and (3) the presence of subcutaneous areas of ossification or calcification. Three of Albright's patients had biopsies of the parathyroid gland, and in two hyperplastic parathyroid tissue was found. In the third patient, who had been on large doses of AT 10, normal parathyroid tissue was found. A similar investigation in seven cases of idiopathic hypoparathyroidism failed to demonstrate parathyroid tissue.

In a review of pseudohypoparathyroidism, MacGregor and Whitehead [*12*] rejected the absence of a response to intravenously administered parathyroid extract as a diagnostic criterion for pseudohypoparathyroidism. They concluded that, in view of the inconsistent response of normal subjects to the extract [*13,14*], the other features of pseudohypoparathyroidism were sufficient to distinguish it from idiopathic hypoparathyroidism. In a case report on pseudohypoparathyroidism [*15*] Albright is quoted as having stated that the Ellsworth-Howard test is quite unreliable in the differentiation of pseudohypoparathyroidism from idiopathic hypoparathyroidism. Bronsky et al. [*8*] found that the phosphaturic action of various parathyroid extracts varied greatly and only with perseverance in testing could it be demonstrated that patients with pseudohypoparathyroidism do not have a phosphaturic response.

Pseudo-pseudohypoparathyroidism is the name Albright, Forbes and Henneman [*1*] chose to describe the syndrome of a patient who had no chemical or physical evidence of hypoparathyroidism but who had many findings similar to those in patients with pseudohypopara-

TABLE II*

THE CLINICAL FINDINGS IN PATIENTS WITH PSEUDO-PSEUDOHYPOPARATHYROIDISM

Case No.	Age, Sex	Height (in.)	Weight	Short Metacarpals and/or Metatarsals	Ectopic Ossification	Basal Ganglial Calcification	Exostoses	Cataracts	Blue Scleras	Mental Retardation	Reference
Case I	29, F	63	169	+	+	−	−	−	−	?	[1]
Case II	24, F	58	187	+	0	−	−	+	−	+	[16]
Case III	40, M	62	120	+	0	−	+	+	+	−	[17]
Case IV	24, M	66	Normal	−†	+	−	−	−	−	−	[18]
Case V	24, M	62	128	+	+	−	+	−	−	+	[6]
Case VI	15, F	59	126	+	0	−	−	−	+	+	[19]
Case VII	11, F	56	77	+	0	−	−	−	+	+	[19]
Case VIII	65, F	56	120	+	+	−	−	+	−	?	[20]

* − = Present.
0 = Absent.
\+ = No information.
† Short distal phalanges.

thyroidism. This patient, a twenty-nine year old white woman, was short and thickset and had a round face. She had short fingers and toes which, on roentgenographic examination, were found to be due to shortened metacarpal and metatarsal bones. She also was found to have extensive subcutaneous bone formation. She had normal serum calcium, phosphorus and alkaline phosphatase levels.

Although this patient was the prototype of pseudo-pseudohypoparathyroidism, patients reported on subsequently have differed in varying degrees from this original patient. Table II compares the salient features of the eight patients with pseudo-pseudohypoparathyroidism reported on [*1,6,16–20*]. It is interesting that one patient reported on by Roche [*17*] had multiple exostoses and very closely resembled some of the members of the family reported on herein.

Several reports [*21–23*] indicate that there is a familial association of pseudo-pseudohypoparathyroidism and pseudohypoparathyroidism, which suggests an even greater similarity in the genetic defects of these two disorders. For example, Frame and Carter [*21*] in the report of a patient with pseudohypoparathyroidism mention that the patient's mother was only 5 feet tall, had a round, full face, soft tissue ossification, no metacarpal changes, and a normal serum calcium level of 9.4 mg. per 100 ml. In a report of several patients with pseudohypoparathyroidism by Cusmano, Baker and Finby [*22*] it is mentioned that the mother of one was 4 feet 8 inches tall, had shortened first, fourth and fifth metacarpals bilaterally, no subcutaneous ossification, and no symptoms suggestive of hypocalcemia. Selye [*23*], in describing a patient with pseudohypoparathyroidism, mentions that the patient's mother had shortened fourth and fifth metacarpals bilaterally, soft tissue calcification and a normal serum calcium level. It is apparent that these mothers of patients with pseudohypoparathyroidism could have been classified as having pseudo-pseudohypoparathyroidism.

Myositis ossificans progressiva was first related to this group of disorders by Elrick et al. [*11*] in a report on pseudohypoparathyroidism. Myositis ossificans progressiva is a disease of infancy or childhood, of unknown etiology, and not associated with any known blood chemical abnormalities. It is characterized by a progressive process of ossification beginning in the soft tissues and spreading to involve connective tissue of intermuscular septa, fascial planes and tendons, finally causing complete immobility of the trunk and extremities [*24–26*]. It, too, is associated with skeletal abnormalities involving the great toe (microdactylia and hallux valgus), the thumbs (microdactylia), and sometimes the middle phalanges of the fifth digits (hypoplasia). It has also been thought to be a familial disorder because it sometimes occurs in more than one member of the same family, and because other members of the families of these patients frequently have developmental osseous defects [*15*]. Albright et al. [*1*] have pointed out the differences in the skeletal abnormalities between

pseudo-pseudohypoparathyroidism and myositis ossificans progressiva. Of especial interest to this report is the frequent occurrence of multiple exostoses in patients with myositis ossificans progressiva. This was noted in the review by Rosenstirn [*24*], and has been commented on subsequently by Singleton and Holt [*25*] who reported a nine year old white boy with myositis ossificans progressiva and prominent multiple exostoses. Although not commented upon, the distribution of the exostoses is much like that seen in hereditary multiple exostoses. Thus this case serves as another link in the chain of these disorders.

Familial calcification of the basal ganglia is a slowly progressive neurologic disorder characterized by massive symmetrical calcification in the basal ganglia, and has been related to this group of disorders because of the frequent occurrence of calcification of the basal ganglia in patients with both idiopathic hypoparathyroidism and pseudohypoparathyroidism. It is not accompanied by other signs or chemical evidence suggesting either idiopathic hypoparathyroidism or pseudohypoparathyroidism. Recently, Matthews [*27*] reported on an entire family with calcification of the basal ganglia, in whom no other abnormalities suggesting hypoparathyroidism or pseudohypoparathyroidism were discovered. In a well controlled Ellsworth-Howard test, using potent parathyroid extract, in one member of this family, no response was obtained. This suggested that the cellular unresponsiveness to parathyroid extract in patients with pseudohypoparathyroidism may exist in patients without abnormalities in their serum calcium or phosphorus levels. Thus familial calcification of the basal ganglia may be another variant of this group of disorders.

Although previously not recognized as such, hereditary multiple exostoses is the most common variant of this group of disorders. The association with myositis ossificans progressiva [*24,25*] and with pseudo-pseudohypoparathyroidism [*17*] has been pointed out. In the latter case, reported by Roche [*17*], there were two other findings, blue scleras and cataracts, which are not usually associated with hereditary multiple exostoses, but which have been reported in other cases of pseudo-pseudohypoparathyroidism. (Table II.) Because of their short stature, round face, metacarpal changes, exostoses and normal response to parathyroid extract, the first and second patients in the family reported on herein might equally well be classified as either pseudo-pseudohypoparathyroidism or hereditary multiple exostoses. The finding of short metacarpals and exostoses without other abnormalities in other members of this family further relates these disorders.

Hereditary multiple exostoses, a subject reviewed by Jaffe [*28*], is a disorder of skeletal formation. Exostoses, which characteristically develop at the sites of bone growth at epiphyseal cartilage plates, are first noticed in early childhood and continue to appear, and grow, until after adolescence. During adult life no new exostoses form. There may also be a shortening of the limbs in relation to the trunk, which is said to be due to dissipation of the longitudinal growth force at the metaphyses [*28*]. In addition, there may be bowing of the bones of the forearm, curvature of the tibia and fibula, and widening of the metaphyseal ends of bones, especially the long bones. Also, there are frequent deformities of the hands and feet [*29*] as a result of exostoses, shortening or irregularities of the metacarpals, metatarsals and phalanges. In this disorder there are no recognized blood chemical abnormalities and no blue scleras, cataracts, tremors or convulsions. It is interesting to note that in 36 per cent of the cases of hereditary multiple exostoses, no family history of the disorder is obtainable. Thus a genetic mutation must be considered, as has been postulated in pseudohypoparathyroidism, pseudo-pseudohypoparathyroidism and the other related disorders.

Another familial disorder, not previously considered related to this group, is multiple epiphyseal dysplasia, which also is characterized by a short thickset stature, abnormalities in bone formation, and metacarpal, carpal and phalangeal changes resulting in short, stubby hands. The disorder, reviewed by Jackson, Hanelin and Albright in 1954 [*30*], consists essentially of irregularities in the formation and structure of the developing epiphyses. Multiple centers of ossification may develop at different times in the same epiphysis, resulting in the characteristic deformities. In this condition, as in hereditary multiple exostoses, there is a widening of the metaphyseal ends of bones. Also, as in hereditary multiple exostoses, the abnormal epiphyseal ossification ceases in adult life.

Another condition, familial brachydactyly, was noted by MacGregor and Whitehead [*12*] to

consist of metacarpal and metatarsal changes identical with those of pseudohypoparathyroidism. They observed also that the bone changes were sometimes accompanied by exostosis formation. Brailsford [*31*], who reviewed the findings in patients with familial brachydactyly, also made similar observations. In a prior report on developmental abnormalities of the skeleton [*32*] he mentioned that stunting of the limbs, sometimes occurs in association with familial brachydactyly. Recently, the occurrence of short metacarpal bones in association with Turner's syndrome has been pointed out [*33*].

In view of the similarity of pseudo-pseudohypoparathyroidism to a spectrum of disorders (Table 1) which includes not only idiopathic hypoparathyroidism and pseudohypoparathyroidism but also myositis ossificans progressiva, familial brachydactyly, epiphyseal dysplasia, Turner's syndrome and, as demonstrated by this family, hereditary multiple exostoses, a serious question is raised as to the advisability of classifying pseudo-pseudohypoparathyroidism as a distinct and separate syndrome. A clearer understanding of these disorders might be obtained by considering them to constitute a spectrum of genetically determined disturbances in bone, calcium and phosphorus metabolism, with or without hypoparathyroidism or derangements in serum calcium and phosphorus levels.

SUMMARY

1. Observations are reported on four generations of a family, eight members of whom manifested the characteristic features of hereditary multiple exostoses.

2. All of the affected subjects had multiple bony exostoses. Two were short-statured, round-faced and had shortened metacarpals, and could have been classified as having pseudo-pseudohypoparathyroidism. Two others had shortened metacarpals without other abnormalities.

3. The Ellsworth-Howard, phosphate clearance and tubular reabsorption of phosphate tests were performed before and after parathormone administration in one subject and a normal response was obtained. The serum chemical findings were normal in all patients studied.

4. The reported cases of pseudo-pseudohypoparathyroidism and the other syndromes which are related to it, or have been likened to it, are reviewed.

5. In view of the similarity of pseudo-pseudohypoparathyroidism to a spectrum of disorders (Table 1) which includes not only idiopathic hypoparathyroidism and pseudohypoparathyroidism, but also myositis ossificans progressiva, familial brachydactyly, epiphyseal dysplasia, Turner's syndrome and, as demonstrated by this family, hereditary multiple exostoses, a serious question is raised as to the advisability of classifying pseudo-pseudohypoparathyroidism as a distinct and separate syndrome. A clearer understanding of these disorders might be obtained by considering them to constitute a spectrum of genetically determined bone, calcium and phosphorus disturbances, with or without hypoparathyroidism or abnormal serum calcium and phosphorus levels.

ADDENDUM

Three other reports which are pertinent to the present discussion have recently appeared [*34–36*].

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The Renal, Cardiovascular, Hematologic and Serum Electrolyte Abnormalities of Heat Stroke*

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ACUTE heat stroke, in its classic form, represents one of the few true medical emergencies which, despite immediate vigorous treatment, continues to impose an unfortunately high mortality on its victims.

The following case is reported because of the number and severity of complications which included extensive myocardial infarction, acute renal insufficiency, jaundice and thrombocytopenia. An unusual opportunity was provided, therefore, to study the interrelationships of these complications over a period of forty-three days during which time the patient underwent artificial hemodialysis on seven occasions. Electrocardiographic manifestations of frank myocardial infarction occurring in heat stroke with demonstration of the absence of coronary artery disease at autopsy has not previously been reported. The association of tubular necrosis with acute renal insufficiency occurs in 2 to 9 per cent of cases of heat stroke [*2,7,8*]. A recent review by Herman and Sullivan [*9*] has emphasized the frequency of jaundice during the course of heat stroke. Halden [*10*], Wilson and Doan [*11*], and Wright and Cuttino [*12*] have studied the occurrence of thrombocytopenia in heat stroke, although disappearance of megakaryocytes from the marrow has not previously been reported.

CASE REPORT

A twenty-three year old white man entered the United States Army in July 1958. He had previously been employed as an outboard motor mechanic in a northeastern city and had no past history of significant illnesses or alcoholism. He negotiated early phases of basic training in a southern state without difficulty but noted the gradual onset of weakness, fatigability, lethargy and anorexia during the fourth week. After several days of these symptoms, while nearing completion of a 10 mile hike, the patient complained of feeling hot and light-headed. Shortly thereafter he collapsed and was immediately taken to the post hospital where a diagnosis of heat stroke was made.

The patient was found to be unresponsive, with an unobtainable blood pressure, rapid and weak pulse, hot dry skin, and a rectal temperature greater than 108°F. The pupils were widely dilated and unreactive to light. The heart sounds were distant but otherwise normal. The lungs were clear and the respirations rapid. The patient was immediately immersed in a tub of ice water and while being massaged was given an infusion of dextrose in normal saline solution containing hydrocortisone and norepinephrine. Shortly after immersion, tonic seizures, vomiting and aspiration of vomitus occurred which necessitated tracheotomy. The patient was removed from the ice bath after ninety minutes when the rectal temperature was lowered to 102.8°F. Three hours after admission the blood pressure was still unobtainable, but after the rapid infusion of 1,500 cc. of dextran, the blood pressure reached 140/80 mm. Hg. Chlorpromazine was given intravenously because of tonic seizures and restlessness. An electrocardiogram showed changes consistent with acute posterior wall myocardial infarction. (Fig. 1.) Blood pressure and pulse thereafter remained near 120/80 mm. Hg and 100, respectively.

Neurologic evaluation five hours after admission

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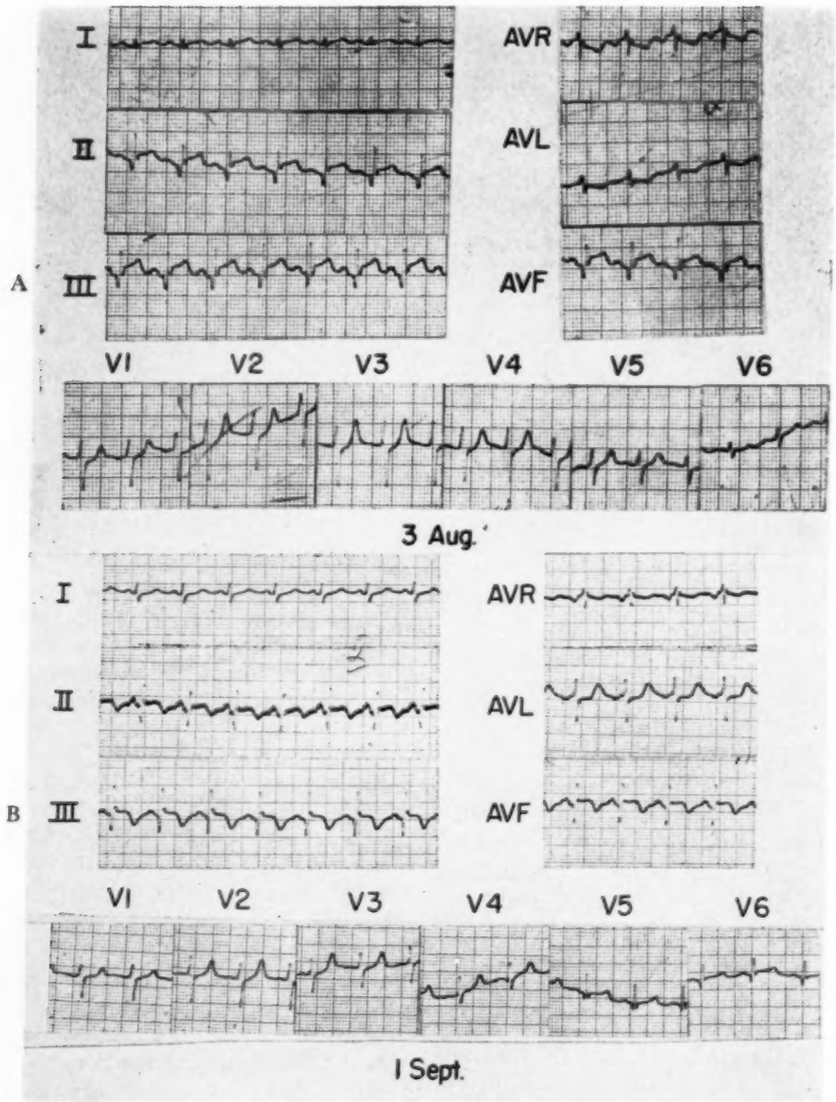


FIG. 1. A, electrocardiogram on admission, showing changes of acute posterior wall myocardial infarction. B, electrocardiogram approximately one month later, showing persistent S-T segment elevation and evidence of lateral extension.

showed smaller, reactive pupils, normal deep tendon reflexes, response to painful stimuli, and occasional brief, tonic muscular contractions with repeated convulsive seizures. A lumbar puncture was performed which showed no abnormalities.

Ten hours after admission the patient was able to answer questions. Petechial hemorrhages had appeared on the eyelids, conjunctivas and thorax. Because of thirst and a total urinary output of only 100 cc. in fourteen hours, 1,000 cc. of 5 per cent dextrose in water was given during a ninety-minute period in an attempt to elicit a diuresis. Shortly thereafter substernal pain, severe dyspnea, diffuse rales and expiratory wheezes were noted. Administration of aminophylline intravenously resulted in rapid improvement. Fluids containing hydrocortisone were continued at a rate of 1,000 cc. every eight hours. During the first twenty-four hours the patient received 5,300 cc. of intravenous fluids with a total urinary output of 225 cc. Urinalysis showed 4-plus proteinuria, microscopic findings of 8 to 12 white cells, innumerable red cells, numerous hyaline and granular casts per high power field and a specific gravity of 1.031.

The second day subcutaneous emphysema developed extending from the tracheotomy wound to the face and abdomen. An x-ray film of the chest demonstrated air in the mediastinum and a 5 per cent left pneumothorax. Scleral icterus and tender hepatomegaly were noted. Because of continuing oliguria the patient was transported by air to this hospital.

Physical examination on arrival forty-nine hours after the onset of illness showed the patient to have a

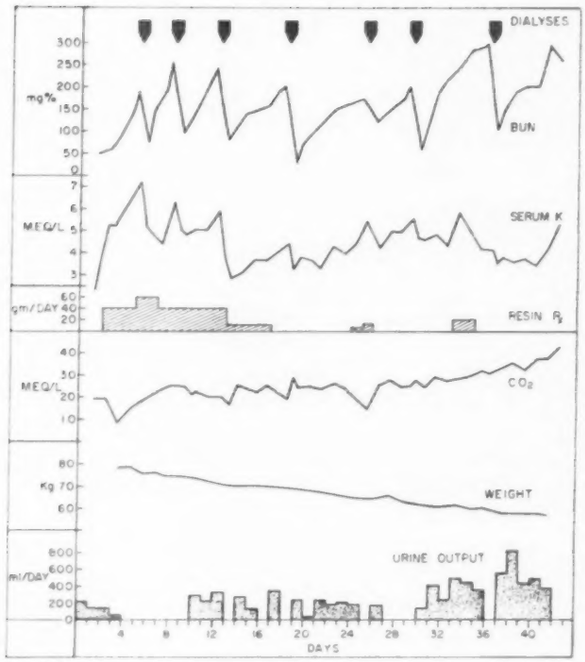


FIG. 2. Chart depicting the course of selected blood chemical values, urine output and weight as influenced by hemodialysis and resin therapy.

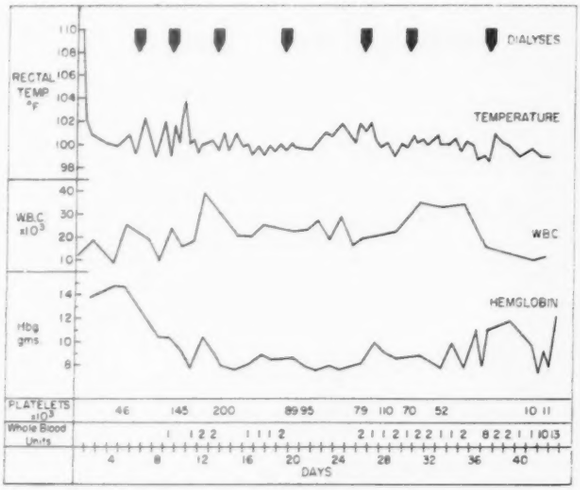


FIG. 3. Chart depicting the course of hematologic data and the instability of body temperature.

temperature of 100°F. rectally, tachycardia of 128 per minute, and a blood pressure of 166/120 mm. Hg. Petechial hemorrhages were scattered over the entire body. Jaundice was moderately intense. The heart sounds were largely replaced by crunching sounds typical of pneumomediastinum. The lungs were clear. There were no retinal hemorrhages or papilledema.

Intravenous 20 to 30 per cent dextrose solution containing vitamins and penicillin was administered continuously in a slow drip, the twenty-four–hour volume being calculated on the basis of daily output and weight. Hydrocortisone was discontinued without difficulty after one day. Testosterone propionate was administered at regular intervals and disodium polystyrene sulfonate resin was given as indicated for hyperkalemia. All dialyses were performed on the rotating drum type artificial kidney for periods of six hours.

Symptoms of uremia were progressive and the first dialysis became necessary on the sixth day of illness. (Fig. 2.) Electrocardiograms showed definite lowering of the T waves, and two hours following the completion of the dialysis the patient became more alert.

Intermittent gastric suction was instituted after the second day of illness because of continuous vomiting of guaiac-positive material. Blood replacement was begun on the ninth day when bleeding and thrombocytopenia worsened. Platelet-rich transfusions produced little apparent benefit. (For hematologic data see Figure 3.)

Occasional elevations of temperature to 102° to 103°F. were controlled by the application of ice packs to the lower extremities. On the ninth day of illness the patient became restless and had two convulsive seizures in rapid succession. Each seizure began with clonic contractions of the right hand which progressed proximally and terminated in a grand mal convulsion. These also caused a rapid rise of serum potassium from 5.2 to 6.4 mEq./L. A temperature elevation to 104°F. immediately followed the seizures, not accompanied by the usual postictal diaphoresis.

Hepatic failure seemed evident that day because of progressive jaundice, a reduction of the previously palpable liver to a total height of 10 cm. by percussion, and increasing abnormalities of liver function. The second dialysis was performed and, although the patient improved, a flapping tremor appeared and the patient remained lethargic. Fetor hepaticus was not noted.

Hemodialysis was again necessary on the thirteenth day for progressive uremia and was complicated by hematemesis. Following this, potassium exchange resins were no longer necessary. A short course of methyltestosterone failed to alleviate pruritus. A transient elevation of blood pressure to 220/130 mm. Hg on the eighteenth day was not accompanied by evidence of myocardial decompensation. By this time the status of his liver had improved as evidenced by a rapid decline of jaundice.

On the twentieth day pain in the right upper quadrant recurred, along with jaundice and enlargement of the liver to 8 cm. below the costal margin. On this occasion there was an eosinophilia of 13 per cent. Chlorpromazine, which had been given in a dosage of 15 mg. every six hours for vomiting, was discontinued. Although the eosinophilia regressed the following day, the liver remained enlarged and jaundice fluctuated in intensity thereafter.

The fifth dialysis was performed on the twenty-sixth



FIG. 4. Extensive transmural infarction involving posterior wall of left ventricle with subendocardial extension into interventricular septum.

day because of symptoms of uremia, again associated with convulsive seizures. During the dialysis the patient again vomited large amounts of blood, had another seizure, and bled considerably from the cutdown sites.

Electrocardiograms continued to show elevation of S-T segments in leads II, III and aVF. A small Q wave with S-T segment elevation appeared in V_6 (Fig. 1), and was considered indicative of lateral extension of the myocardial necrosis.

The sixth dialysis on the thirtieth day of illness was again complicated by gastrointestinal bleeding. Temperature elevations occurred almost daily and were accompanied by mild to marked leukocytosis. Administration of Chloromycetin® was begun on the thirty-second day because of positive blood cultures for Alkaligenes fecalis and the paracolon bacillus. On the thirty-seventh day, dialysis was performed for the seventh time. Massive hematemesis during the procedure required replacement with 4,000 cc. of blood.

Late in the hospital course, compensated metabolic alkalosis was noted, manifested by hypochloremia, hypokalemia, hypercapnia and hypernatremia. Clinical signs of alkalosis did not appear and the blood pH remained in the neighborhood of 7.4. There were no electrocardiographic changes of hypokalemia. Potassium administration was begun.

On the forty-second day massive hemorrhage occurred from the gastrointestinal tract. The patient continued to bleed uncontrollably and became progressively hypotensive despite the administration of vasopressors and large amounts of blood. He died in irreversible shock on the forty-third day of his illness.

Throughout the hospital course the sites of venous and arterial cutdowns failed to heal. After the second week the microhematuria decreased and after the fourth week broad "renal failure" casts appeared in large numbers. The specific gravity of the urine, although 1.031 on the first specimen, remained at 1.010 throughout the subsequent course. Values for serum creatinine varied from 8.5 to 22.4 mg. per cent, calcium from 3.4 to 5.5 mEq./L. and serum phosphorus from 3.5 to 10.3 mg. per cent. The daily urinary output is tabulated in Figure 2.

Autopsy Findings. Examination of the heart disclosed a softened area 5 cm. in diameter on the posterior left ventricular wall which extended around the lateral wall and into the interventricular septum. (Fig. 4.) There were, in addition, smaller foci of necrosis in the left ventricle, both subendocardially and scattered transmurally in the lateral wall. The heart weighed 320 gm. There were no gross abnormalities of the coronary arteries. Microscopically the posterior left ventricular wall showed extensive areas of myocardial infarction. In some areas there were small amounts of connective tissue replacement while others showed findings consistent with more recent infarction. Even the small coronary arteries were normal and on careful dissection showed no evidence of atheromatous plaques. The bone marrow was hypercellular with erythroid hyperplasia and almost total absence of megakaryocytes.

The esophagus showed extensive mucosal ulceration. The stomach also was the site of multiple mucosal erosions measuring up to 2 cm. in diameter, most marked in the antral and prepyloric regions. In the center of one ulceration a medium-sized artery was eroded, the most obvious source of gastrointestinal bleeding.

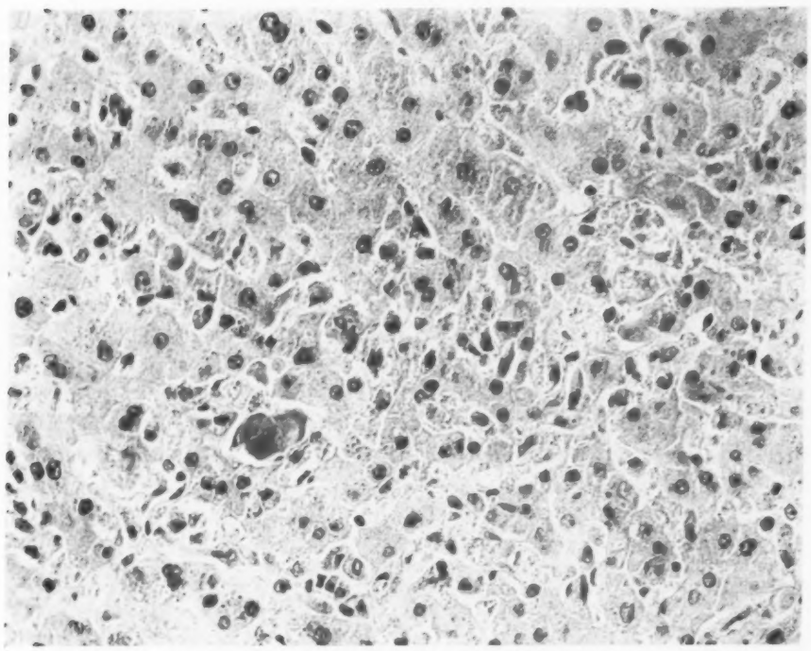


FIG. 5. Liver, showing bile stasis with good preservation of parenchymal cells.

The liver weighed 1,840 gm. and grossly appeared to be congested and extensively stained with bile. Microscopically there was no evidence of significant necrosis or parenchymal collapse, as substantiated by reticulum stains. Extreme bile stasis was evident in the central portion of the lobules, in which numerous bile thrombi and bile lakes were seen, and in the portal areas where the small bile ducts were dilated and plugged with dark bile. (Fig. 5.) The hepatic cells appeared to be well preserved.

The pancreas grossly and microscopically showed evidence of fat necrosis and extensive inflammatory changes especially in the head although there was no apparent compression of the common bile duct.

The right kidney weighed 200 gm. and the left 245 gm. The capsules were tense but stripped with ease. The underlying cortices were smooth. Cross sectioning showed marked congestion and bile staining. The corticomedullary junction was obscure. Microscopically the glomeruli were well preserved, without evidence of inflammatory change. The tubules showed a low regenerative epithelium which in places had papillary projections. Scattered heme casts and numerous bile-stained casts were present in the tubules, especially in the loop of Henle. Interstitial inflammation was minimal. The adrenal glands showed no remarkable abnormality. The brain weighed 1,305 gm. and appeared slightly congested. Despite the patient's clinical symptomatology there were no significant microscopic abnormalities.

COMMENTS

In studying cases of heat stroke as they occur in military and civilian life a distinct difference in the clinical setting is noted between the two groups. Outside of the military, most cases are seen in older persons who often have arteriosclerosis, heart disease or acute alcoholism [*1,2*]. Heat stroke also occurs with increased expectancy in children suffering from fibrocystic disease [*3*] and in those who are unable to sweat effectively. Among the latter group are persons having congenitally absent or defective sweat glands [*4*] or patients undergoing surgical procedures who have been heavily draped following the use of atropine or drugs of similar action [*5*]. In the Army, heat stroke is most frequently seen in young persons in basic training. Certain investigators [*6,7*] have stressed the lack of adequate acclimatization to a hot environment as an important factor in its development. The numerous complications in this case occurred despite the patient's youth and apparent good health.

Renal Failure in Heat Stroke. Acute renal tubular necrosis complicates heat stroke in 2 to 9 per cent of cases [*2,7*] and its incidence, as in this case, appears related to the degree of hyperpyrexia and prolonged shock. The usual cause of death in cases previously reported has been fulminating hyperkalemia incident to massive tissue necrosis and the marked catabolic response which is a frequent early feature of acute renal failure. Failure to recognize this renal complication early in the course of treatment probably

explains the tendency to overhydrate such patients.

In reporting 125 fatal cases of heat stroke, predominantly among recruits in Army Basic Training, Malamud [*7*] noted that 60 per cent had hypotension and the fatal outcome correlated best with the incidence of shock. The pathologic findings of acute tubular necrosis were noted only in those surviving more than twenty-four hours, and represented an incidence of 9 per cent.

In Austin and Berry's report of 100 cases of heat stroke [*2*] two deaths were ascribed to "anoxic nephrosis." A "poor-risk" patient showed a temperature greater than 106°F., coma, azotemia, hypotension and hyperkalemia. Azotemia occurred in twenty-nine patients, with nine deaths, a mortality of 31 per cent. Hypotension was attended by a 33 per cent mortality. Hyperkalemia occurred in only four patients, two of them azotemic; however, all four died.

Baxter and Teschan [*8*] reported three fatal cases of heat stroke with oliguria. Deaths were attributed to shock, persistent hyperthermia and a remarkably rapid rise of plasma potassium concentration with fulminating potassium intoxication.

Austin and Berry's data [*2*] on the characteristics of the urinary abnormalities lead one to conclude that the sign most suggestive of acute renal failure in heat stroke is oliguria. These authors report a specific gravity of the urine as less than 1.020 in 72 per cent, albuminuria in 60 per cent, pyuria in 20 per cent and elevation of the blood urea nitrogen in 42 per cent of the cases. Oliguria was present in the case presented herein from the onset of his illness and was a manifestation of acute renal failure due to acute tubular necrosis. It is suggested that the possible development of renal failure be considered in every case of heat stroke and careful attention be given to urinary output. If the patient fails to excrete urine after shock has been corrected, diagnostic steps and treatment should be instituted on the assumption that the patient has incurred acute renal failure.

Once the diagnosis of acute renal failure was recognized in this patient, fluids were administered on the basis of daily weight together with the previous day's total fluid output. Failure to lose approximately 0.4 kg. daily in the presence of a continuing catabolic preponderance is an indication that fluids are being given in excessive and disproportionate amounts to the progressively decreasing tissue mass. The use of hydrocortisone during the first three days of illness in this patient may have enhanced the expected catabolic response seen especially in the early stages of acute renal failure. It is doubtful if the use of corticosteroids in the treatment of heat stroke exerts a beneficial effect [*14*].

Sweating, which is absent during the acute stage of heat stroke in most cases, reappears after twenty-four to seventy-two hours [*1,7*]. In this case sweating did not reappear during the entire subsequent course of illness. Despite a convulsive seizure followed by a temperature of 104°F. on the ninth day, the usual postictal sweat was absent. This increased the problems of fluid balance because of a decreased insensible loss and impaired temperature regulation.

Electrolyte Derangements. With increasing use of flame photometry, reports of serum electrolytes in heat stroke have disclosed remarkable changes, especially with regard to serum potassium. In this case, as in many others in which serum potassium values have been reported in the early stages of heat stroke, the serum potassium was noted to be low [*1,2,7,8*]. In most instances serum CO_2 likewise is depressed and, although no values for blood pH have been reported, it is very likely that this combination could be the result of respiratory alkalosis secondary to the hyperventilation of hyperpyrexia. The association of alkalosis and hypokalemia without respect to total body potassium has been well described [*15*].

From another viewpoint, however, there exists a distinct theoretic possibility that a patient with heat stroke may have incurred a potassium deficit, as an explanation for the hypokalemia, prior to the onset of hyperpyrexia. Conn et al. [*16–18*] have shown that in the process of acclimatization to heat the adrenal cortex plays a definite role in renal conservation of sodium and, concomitantly, urinary excretion of potassium may increase to amounts exceeding the normal. These authors have shown further that potassium is lost in an amount which is excessive to the expected loss calculated from nitrogen excretion.

When sodium was withheld from normal persons during acclimatization to a hot environment the kidneys were able to respond by conserving sodium, but potassium excretion continued. Although sodium virtually disappeared from the urine within a few days [*16*], potassium continued to be lost in large amounts

over a period of two weeks. A total body potassium deficiency of 200 to 300 mEq. occurred during a similar period of time with sodium restriction alone [*20*].

Schwartz and Thaysen [*21,22*] have shown that during acclimatization to heat, loss of sodium in sweat increased progressively at first but then decreased. Potassium losses also increased but failed to decrease as did sodium, until finally the potassium concentration in sweat reached values averaging 9.4 mEq./L. Robinson and Robinson [*23*] presented evidence suggesting that increased adrenocortical activity associated with adaptation of sodium restriction may increase the loss of potassium in both sweat and urine. It has also been demonstrated that a negative nitrogen balance develops during acclimatization [*18*], usually accompanied by potassium depletion.

The possible role of aldosterone in this instance is uncertain. It has been shown that sodium restriction with an otherwise normal diet will result in increased aldosterone output [*24*], however simultaneous potassium deficiency nullifies this effect [*25*].

Ladell and Waterlow [*6*] noted that in many British soldiers exposed to extreme environmental temperatures polyuria developed, with a urine of low specific gravity, which was resistant to administration of Pitressin.® In their experience this polyuria was noted up to three days prior to the onset of heat stroke in numerous cases and persisted for a time in those who survived. A similar Pitressin-resistant polyuria can be provoked by potassium deficiency in man [*20*].

Unfortunately, all studies in the past with regard to potassium balance have been performed on persons who had not incurred actual heat stroke. Nevertheless, it is entirely possible that hypokalemia may constitute an integral factor in the development of the manifestations of heat injury. This is entirely consistent with such manifestations as weakness, lethargy, isosthenuria and Pitressin-resistant polyuria.

Although the serum potassium was 2.3 mEq./L. during the early stage in the case herein presented, it was supplanted by the rapid development of hyperkalemia. Hyperkalemia is common to both acute renal insufficiency and severe heat stroke separately [*2,8*]. Prior to the first dialysis, it was necessary to use intravenous dextrose, calcium and insulin in addition to oral resins to lower serum potassium.

Convulsive seizures on the ninth day after illness led to a rapid rise of serum potassium from 5.2 to 6.4 mEq./L. Elevation of serum potassium is a constant feature of a sudden decrease of plasma pH [*15*], which in this instance was a consequence of transient anoxia during the convulsion. Such sudden elevations of serum potassium following a seizure in a uremic patient may precipitate fatal cardiac arrhythmia.

Following the second dialysis on the ninth day, the serum CO_2 returned to a normal value and remained stable until the thirty-third day when it began to rise progressively. This appeared to be a manifestation of a combined hypokalemic and hypochloremic alkalosis. Resin therapy, frequent hemodialysis and continuous vomiting necessitating gastric suction were all thought to be contributory factors in depleting the patient of potassium, hydrogen and chloride ions. In spite of a fall of serum chloride to a low of 71 mEq./L. and an elevation of serum sodium to 156 mEq./L. the patient showed no clinical signs of alkalosis and the serum pH remained normal. Electrocardiographic changes of hypokalemia did not appear. One author [*34*] recently attempted to correlate the elicitation of diuresis with potassium replacement therapy in a patient with ostensible acute renal failure. Although hypokalemic nephropathy has been said to occur in the recovery phase of acute tubular necrosis [*20,35*], the latter, to our knowledge, has never been directly attributable to hypokalemia *per se*.

Myocardial Damage in Heat Stroke. Malamud et al. [*7*] reported subendocardial hemorrhages which showed a predilection for the left side of the interventricular septum. There were hemorrhages into the cardiac muscle in one-fifth of his cases and, occasionally, massive extravasation of blood into the myocardium. Fragmentation and rupture of muscle fibers was conspicuous in well over one-fourth of the cases. Wilson [*27*] reported subendocardial hemorrhages in the septal region of the left ventricle in four cases.

Myocardial necrosis in this case was thought to be secondary to extensive hemorrhages directly into the myocardium, although it is possible that necrosis was secondary to a marked diminution of effective blood volume [*28*]. The apparent failure of resolution of the area of hemorrhagic infarction was reflected clinically by the persistence of S-T segment elevation in serial electrocardiograms and was confirmed pathologically. The marked failure of healing could best be explained on the basis of severe

prolonged uremia [*36*]. This finding correlated well with the failure of healing in the numerous cutdown sites, even those of forty-three days' duration. The complete absence of coronary artery disease was striking. In this case, as in the majority of other reports concerning myocardial damage in heat stroke, there was involvement of the left side of the interventricular septum. (Fig. 4.) The explanation for this peculiar localization is not apparent.

Daily and Harrison [*28*] have shown by animal experiments that the cardiac output doubles with a rise in temperature from 37° to 42°C., but falls rapidly at higher temperatures. Oxygen consumption behaved in a similar fashion, showing a progressive increase up to 42.4°C., followed by a sharp decline which implied a marked tissue anoxia. Venous pressure was not elevated in these experiments unless significant amounts of fluids were given. Circulatory collapse was shown to be predominantly peripheral in nature but attended by a definite impairment of cardiac reserve. In contrast to this experimental finding, two of us (W. R. B. and E. G. H.) have observed markedly distended peripheral veins and pulmonary edema in patients with acute heat stroke who had received no intravenous fluids and had no pre-existing cardiac disease. Ordinarily, simple reduction of body temperature by ice bath immersion and vigorous massage of the extremities will improve circulatory hemodynamics in patients who go on to recovery. In the case presented, the blood pressure failed to return to normal levels and remained unobtainable for at least three hours despite control of hyperthermia.

Administration of intravenous fluids to a patient with heat stroke may precipitate pulmonary edema. Aged persons and others with compromised myocardial reserve would be especially liable to such a complication.

To explain pulmonary edema in the untransfused human subject with heat stroke Daily and Harrison [*28*] postulated four factors: (1) pre-existing cardiac insufficiency; (2) hyperpnea inducing decreased intra-alveolar pressure with an increased passage of fluid through the already heat-damaged, engorged pulmonary capillaries; (3) diminished coronary blood flow incident to decreased venous return with left ventricular failure and (4) overenthusiastic treatment with intravenous fluids. We would add cardiac failure due to direct myocardial damage to this list, based on our clinical experience and the not uncommon occurrence of hemorrhagic myocardial necrosis in heat stroke. The use of norepinephrine leads to cutaneous vasoconstriction and directly impairs the transfer of heat from deeper tissues to the skin. In addition, the use of corticosteroids in conjunction with vasopressors, although of proved value in some cases of refractory shock, should be attempted only with extreme caution in view of the excessive splanchnic vasoconstriction due to their synergistic effect [*29,37*]. In short, heat stroke is best managed by rapid cooling, to be followed by vasopressors only in the event that shock does not respond to correction of hyperthermia.

Electrocardiographic Changes. Logue [*30*] reported on the electrocardiographic changes in three cases of heat stroke; these consisted solely of T wave abnormalities that returned to normal within three months. Herman and Sullivan's patient [*9*] also showed T wave inversion in leads II, III and aVF which reverted to normal in four months.

Metz [*31*] reported three cases of myocardial injury in heat stroke occurring in German soldiers whose ages were twenty-two, twenty-three and thirty years, respectively. The first patient showed electrocardiographic changes of acute left bundle branch block which reverted to normal in eight months. At that time a stress test produced T wave inversion and ventricular premature contractions. The second subject showed transient T wave abnormalities and the third was interpreted as having changes indicative of posterior myocardial infarction. The latter patient was obese and intoxicated at the time of onset. Since all these patients recovered, it remains unknown whether or not coronary atherosclerosis was present.

Although electrocardiographic findings have not been adequately reported in many of the large series of cases of heat stroke, it is entirely possible that changes of myocardial infarction are not unusual.

Injury to the Liver. In the patient herein recorded, evidence of hepatic damage became apparent thirty-six hours after admission and was manifested by jaundice, hepatomegaly, and pain and tenderness in the right upper quadrant. The icterus steadily increased in intensity until the seventh hospital day. However, on the ninth day there was another rapid rise in serum bilirubin to 34.8 mg. per cent which was accompanied by a decrease in the size of the liver,

progressive lethargy, transient appearance of a flapping tremor, and laboratory values consistent with acute injury to the liver. Although massive hepatocellular collapse seemed evident, it was not possible to differentiate between the symptoms of impending hepatic coma and uremia.

Another rise of serum bilirubin on the twentieth day, associated with a recurrence of hepatomegaly and eosinophilia, was suggestive of chlorpromazine toxicity although liver function studies failed to suggest biliary obstruction. While eosinophilia may have been a manifestation of chlorpromazine hypersensitivity in this patient, Halden [*10*] reported eosinophilia during the initial phase of heat stroke in thirteen of fifteen patients. There was no clinical suggestion of pancreatitis in this patient; however, it is possible that the presence of acute suppurative lesions in the head of the pancreas could have contributed to jaundice by compressing the common bile duct.

The occurrence of hyperbilirubinemia and clinically apparent jaundice in heat stroke is common. As a rule, liver function returns to normal with recovery. For a complete discussion of hepatic injury in heat stroke the reader is referred to a recent review on the subject [*9*].

Hematologic Abnormalities. Hemorrhagic manifestations comprised an important aspect of this patient's illness. Petechial hemorrhages were apparent on the first day and cleared completely over a period of seven days without recurrence in spite of thrombocytopenia. Gastrointestinal bleeding became progressively more severe and finally accounted for his death.

There was a transient improvement in thrombocytopenia by the tenth day; however, after the twentieth day, platelets again decreased progressively. The cause of the second fall in platelets is inapparent but could well have been due to drug sensitization. This was especially suggested by the appearance of an eosinophilia of 13 per cent on the twentieth day with the additional development of hepatomegaly, pain in the right upper quadrant and progressive rise of total serum bilirubin.

Exacerbations of leukocytosis up to 38,500 per cu. mm. on several occasions could not be correlated with dialyses or positive blood cultures. The total white blood cell count approached normal values during the last six days of his illness when blood cultures were positive for the paracolon bacillus and A. fecalis. Bluemle, Webster and Elkinton, in reporting their experience with 100 cases of acute tubular necrosis, noted that leukemoid reactions were rather common, with total white blood cell counts exceeding 30,000 per cu. mm. in 18 per cent of their patients. Such values did not yield accurate information as to the presence or absence of infection, and bore no relation to the eventual outcome of the individual case [*36*].

A component of the hematologic manifestations in this case was the presence of numerous reticulocytes, normoblasts, myelocytes and metamyelocytes in the peripheral smears. This was thought to be unusual, in view of the known inhibitory effect of both uremia and blood transfusions on erythropoiesis. Reticulocytosis averaging 16 per cent was observed in this patient and was thought to be consistent with a significant hemolytic state.

Halden [*10*] studied fifteen patients with heat stroke with the aid of autotransfused Cr^{51} tagged red cells and, in the absence of detectable blood loss, demonstrated a significant decrease of the red cell survival in thirteen instances. All showed thrombocytopenia, and during the initial phase of their illness all showed an unexplained absolute increase in eosinophil count. It was his conclusion that the development of anemia in the course of heat stroke was due both to hemolysis, possibly secondary to capillary stasis, and to direct injury to the bone marrow.

The persistent high reticulocytosis in this patient appeared to be a response to hemolysis, since reticulocytosis of this degree is seldom seen as a response to hemorrhage or during the recovery phase from iron deficiency anemia [*38*]. To what extent hemolysis contributed to jaundice was difficult to ascertain since bilirubin fractionation varied from day to day between predominantly direct to predominantly indirect, and primary hepatic damage was present.

The use of dextran in the treatment of shock in the early stage of heat stroke may be fraught with considerable danger. Langdell et al. [*32*] have shown that dextran has a direct inhibitory effect on the function of platelets when given in significant amounts. In the presence of thrombocytopenia, even slight impairment of platelet function by dextran may have devastating effects [*32*].

Several investigators [*7,10–12*] have demonstrated acute megakaryocytic injury, thrombocytopenia, purpura and decrease of prothrombin concentration, the latter secondary to hepatic damage, during the course of heat stroke.

Bluemle et al. [*36*] recorded abnormalities of coagulation manifested by heparin sensitivity and abnormalities of prothrombin consumption, thromboplastin generation, clotting time, heparin titration, one-stage prothrombin, accelerator globulin, clot retraction and thrombocytopenia in their series of patients with acute tubular necrosis, although no major statistical difference was found between bleeding and nonbleeding patients. In our case, the prothrombin during the initial period of illness was 33 per cent, which upon subsequent determinations showed a return to normal values. Coagulation factors V and VII were normal. Thromboelastograms and prothrombin consumption were both abnormal, and consistent with the degree of thrombocytopenia.

Wright [*12*], in describing twelve cases of heat stroke, postulated a precipitation of proteins involved in blood coagulation, and others [*7,11*] have stressed the importance of anoxia productive of direct capillary damage, as contributory factors in the production of the hemorrhagic complications of this disorder.

SUMMARY

An illustrative case of severe heat stroke complicated by acute renal failure, jaundice, acute myocardial infarction and marked hematologic abnormalities is presented. A review of the pertinent literature is included for the purpose of clarification of the diverse interrelationships of the various complications. Evidence is presented which suggests that total body potassium deficiency may be of etiologic importance in the genesis of heat stroke.

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Eosinophilic Leukemia*

Report of a Case, with Review and Classification

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EVEN though eosinophilic leukemia is accepted by most authorities as constituting a definite entity, its infrequency and the difficulty in establishing a proper diagnosis has made many people reluctant to accept it as such. This hesitancy no doubt is intensified by the marked eosinophilia that patients may manifest either from benign stimuli or directly related illnesses as malignancies, myelogenous leukemia and Hodgkin's disease [*1–9*]. Despite this difficulty, however, support for the concept of an eosinophilic leukemia is provided by numerous, well documented cases and reviews [*10–13*].

The purpose of this paper is to present a case with findings which meet the specific criteria necessary to establish a diagnosis of eosinophilic leukemia. The criteria used in this report are a marked eosinophilia in the peripheral blood with blast cells above normal in the bone marrow and/or peripheral blood during the course of the illness.

Since the diagnosis of eosinophilic leukemia is difficult to establish at the time of onset, the clinical and pathologic variations in the early course of the disease are detailed. A clinical and laboratory picture is thus established which is characteristic and makes the early diagnosis of eosinophilic leukemia possible.

CASE REPORT

The patient was a five year old boy who had been well until October 6, 1958, when he had a sudden onset of fever (temperature of 102°F.) accompanied by a red, serpiginous rash on his legs and torso. During the next three days a generalized, petechial rash and coma gradually developed. Neurologic examination at that time revealed the head turned to the right, arms held in flexion, legs in extension, ankle clonus and bilateral Babinski reflexes. The liver and spleen were not palpable and there was no lymphadenopathy. A hemoglobin determination was 8 gm. per cent, a platelet count was 60,000/cu. mm. and the white blood cell count was 185,000/cu. mm. The white cell differential showed 9 per cent polymorphonuclear neutrophils, 6 per cent lymphocytes, 64.6 per cent polymorphonuclear eosinophils, 17 per cent eosinophilic metamyelocytes and 3.4 per cent eosinophilic myelocytes. A bone marrow biopsy specimen revealed that there were 18 per cent polymorphonuclear neutrophils, 10 per cent lymphocytes, 41.5 per cent polymorphonuclear eosinophils, 12.9 per cent eosinophilic metamyelocytes, 13.6 per cent eosinophilic myelocytes and 4 per cent erythroid elements. The protein, glucose, cell count and pressure of the spinal fluid were within normal limits.

The child was given cortisone 50 mg. every six hours and a single transfusion of whole blood. In ten days he had made a complete recovery, with the neurologic examination, white cell count and differential in the peripheral blood being within normal limits.

He did well clinically following this episode but a constant eosinophilia of 20 to 30 per cent soon developed which persisted for approximately two months. At this time nodules were observed over both parietal bones. Cervical and axillary lymphadenopathy became prominent. A biopsy specimen of a parietal nodule showed sheets of lymphoid cells in the dermis and subcutaneous tissue. These cells had large reticular nuclei with some variation in size. Also there were many developing eosinophils which appeared to be coming from the reticulum. (Fig. 1.)

The patient was then referred to the University of Minnesota Hospitals on January 9, 1959, three months after the onset of his illness. Additional history at this time revealed that a tonsillectomy had been performed four months prior to the onset of illness, with

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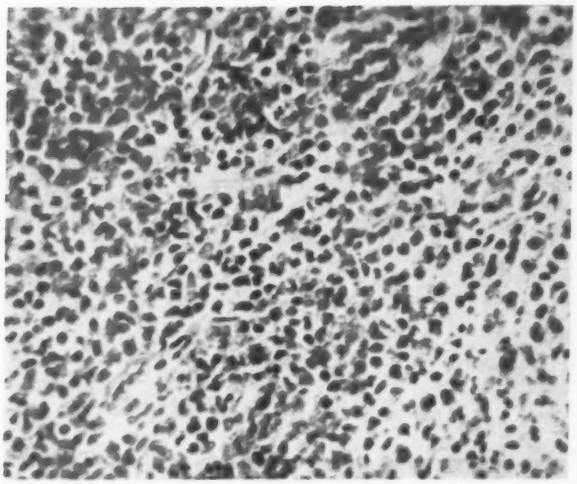


FIG. 1. Microscopic view of parietal nodule.

a pathologic report of "normal tissue." Environmental study showed that he lived on a farm where he was exposed to many animals and that the cows had "screwworm" infestation.

Physical examination revealed lymphadenopathy in the cervical, axillary and inguinal areas. The liver was palpable 8 cm. below the right costal border and the spleen was palpable 2 cm. below the left costal border. Examination of the parietal nodule biopsy site with a Wood's light did not reveal any fluorescence.

The laboratory data on admission were: Hemoglobin 13.8 gm. per cent; white blood cell count 185,000/cu. mm., with a differential count of 12 per cent polymorphonuclear neutrophils, 2 per cent monocytes, 9 per cent lymphocytes, 61.6 per cent polymorphonuclear eosinophils, 11.4 per cent eosinophilic metamyelocytes, 3 per cent eosinophilic myelocytes and 1 per cent basophils. A bone marrow aspiration gave a differential count of 18 per cent polymorphonuclear neutrophils, 8 per cent neutrophilic metamyelocytes, 6 per cent neutrophilic myelocytes, 2 per cent neutrophilic promyelocytes, 25.8 per cent polymorphonuclear eosinophils, 3.1 per cent eosinophilic metamyelocytes, 14.2 per cent eosinophilic myelocytes and 13.4 per cent eosinophilic promyelocytes. Repeated stool examinations for ova and parasites were negative.

The child was started on Myeleran® at a dose of 4 mg. a day. On the nineteenth hospital day a persistent, dry cough developed associated shortly with rapid, labored respirations. A roentgenogram of the chest showed irregular linear infiltrates throughout both lung fields. (Fig. 2.) Myeleran therapy was then discontinued and cortisone therapy reinstituted.

Additional roentgenograms of the chest revealed increased spread of the large patchy densities throughout both lung fields. The child was acutely ill for three days but then gradually improved and by the twenty-fourth hospital day he was free of dyspnea. Because of



FIG. 2. Roentgenogram of the chest showing leukemic infiltrate.

the persistence of the infiltrate in the lung fields, he was given radiation (120 r) to the lung fields and started on 6-mercaptopurine (2.5 mg./kg./day). Following this there was some resolution of the pulmonary infiltrates, and the patient's condition improved for a short time. However, he soon became progressively ill, with resumption of his dyspnea.

The peripheral blood and marrow changed to principally a myeloblastic form. The bone marrow contained 85.3 per cent myeloblasts, 8.7 per cent

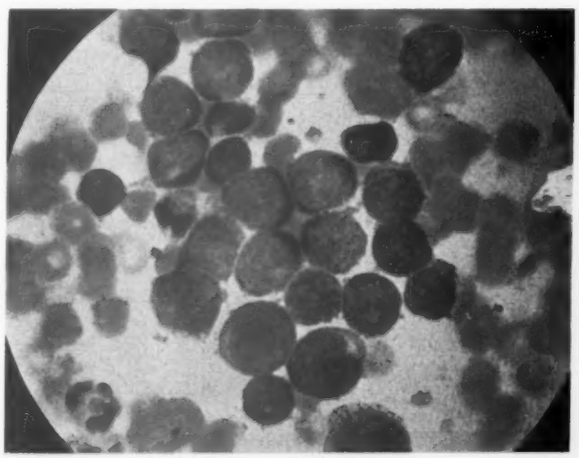


FIG. 3. Microscopic view of the bone marrow showing myeloblastic proliferation.

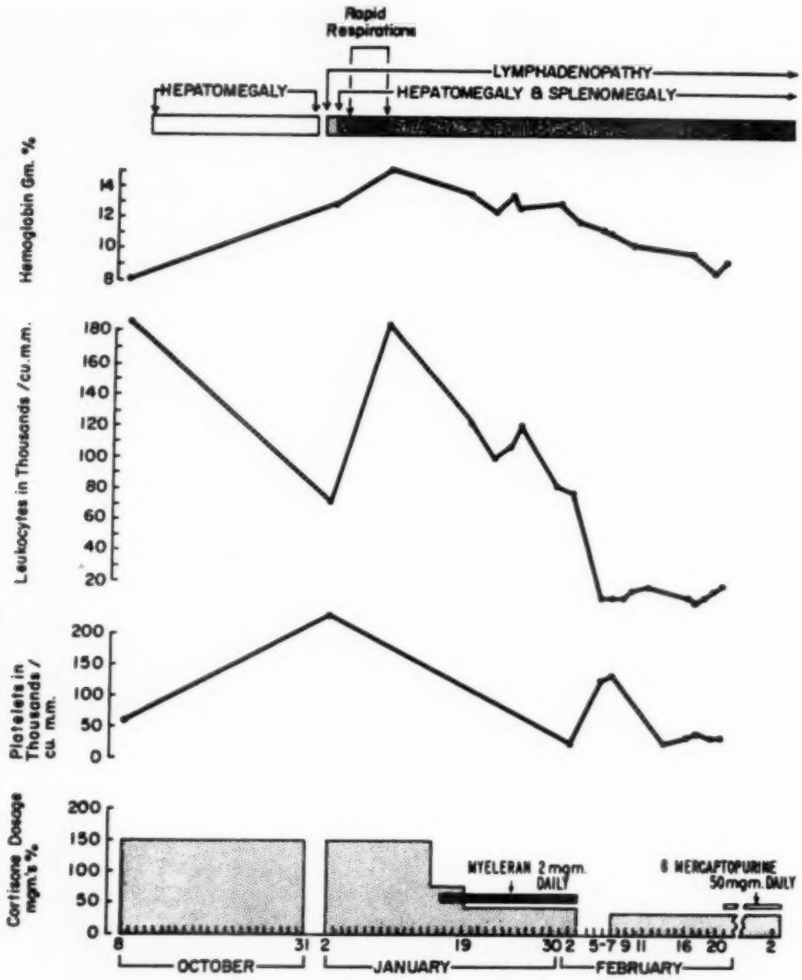


FIG. 4. The clinical and laboratory course of the patient.

eosinophilic leukoblasts, 3 per cent eosinophilic promyelocytes, 1.6 per cent eosinophils, 0.7 per cent lymphocytes and 0.7 per cent erythroid elements. (Fig. 3.) Despite continued therapy the disease pursued a relentless course and the patient died seven months after the onset of the illness. His course and laboratory work are summarized in Figure 4.

Postmortem Examination. The face was moonshaped. A small crusted area was noted to the left of the mouth and numerous petechiae were seen over all the body surfaces but particularly over the lower extremities. No pitting edema was noted although the lower extremities were puffy in appearance.

The heart weighed 140 gm. All the chambers were normal. The myocardium showed numerous petechiae and several tiny areas of scarring in the substance of the myocardium of the left ventricle. None of these areas measured more than 0.5 cm. in diameter. Microscopic sections revealed a mural thrombus of the left ventricle in addition to the areas of scarring where there were numerous macrophages and active fibroplastic proliferation. (Fig. 5.)

The right lung weighed 380 gm., the left 300 gm. The bronchial tree showed an increased amount of rust colored frothy fluid. Hemorrhagic areas were demonstrable throughout but were most marked in the lower lobe of the right lung. Microscopic examination showed pulmonary edema and myeloblast infiltration.

The liver weighed 1,100 gm. and was yellow-brown in color. No gross changes were evident. Microscopic examination revealed blast cell infiltrate in the portal area. (Fig. 6.) The spleen weighed 230 gm. The capsule was thin and smooth and the parenchyma was a deep red color. There was normal follicle formation on cut section, but microscopic examination showed complete destruction of the architecture by blast cells. (Fig. 7.) The stomach was markedly dilated. Petechiae were frequent in the stomach and a few petechiae were noted throughout the remainder of the gastrointestinal tract. Microscopic examination showed minimal blast cell infiltrate of the stomach and colon.

The right kidney weighed 80 gm., the left 70 gm. A few petechiae were noted throughout the parenchyma



FIG. 5. Microscopic view of scarred areas of the myocardium.

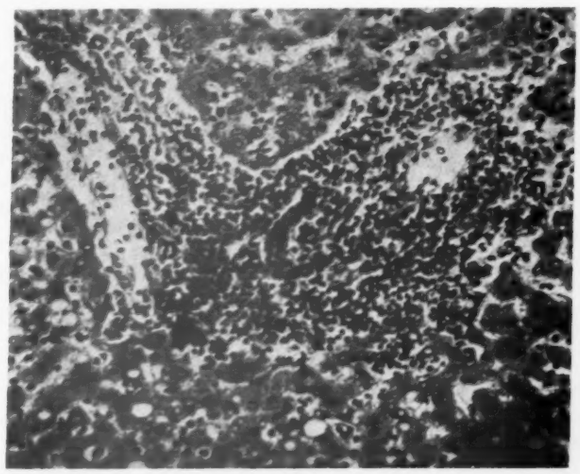


FIG. 6. Microscopic view of the blast cell infiltrate of the portal area of the liver.

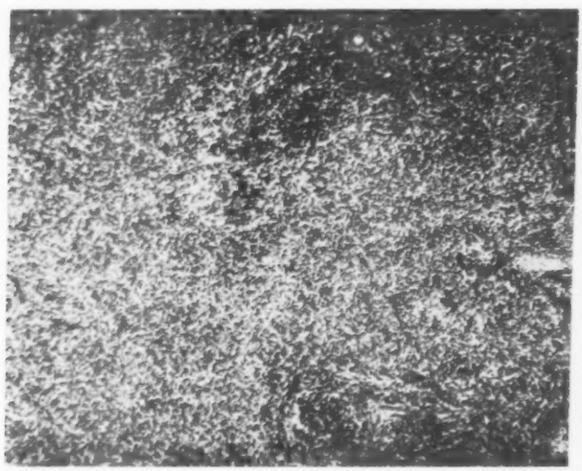


FIG. 7. Microscopic view of the spleen showing destruction of the normal architecture by blast cells.

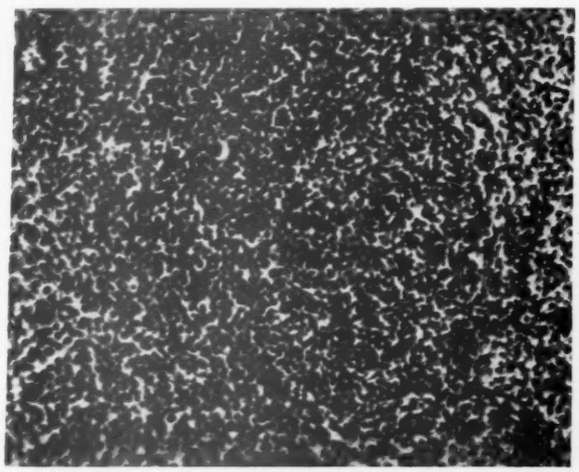


FIG. 8. Microscopic view of a lymph node showing blast cell infiltration.

of the two kidneys. Microscopic examination showed minimal blast infiltrate of the kidneys and the urinary bladder.

Nodes in the periaortic, peripancreatic, anterior mediastinum and hilar areas were enlarged with varying degrees of blast cell infiltrate seen on microscopic examination. (Fig. 8.)

Grossly the meninges and brain were normal but microscopic examination showed minimal blast cell infiltrate.

Microscopic examination of the testes showed minimal blast cell infiltrate.

REVIEW OF THE LITERATURE

A review of the literature reveals that cases of eosinophilic leukemia which meet the general criteria of leukemia [*14,15*] may be divided into two groups: (1) eosinophilic leukemia beginning with increased blast cells in the peripheral blood and/or bone marrow (Table I)* and (2) mature cell eosinophilic leukemia with an acute or chronic course. (Table II.)*

As noted in Tables I and II, nine cases were of the acute blastic type, five patients had mature cells on presentation but assumed an acute course, and six cases represented a true chronic leukemia with protracted clinical course.

It is evident then that eosinophilic leukemia

* These tables do not contain several reported cases [*35–42*] as these journals were not available to us. Also, they do not include several cases which have been reported as eosinophilic leukemia but by the established designations for diagnosis could not be accepted as such [*11,43–79*]. These probably represent other diseases which show a qualitative increase in eosinophils without the cytologic criteria of leukemia, and have been termed "eosinophilic leukemoides."

establishes clinical patterns similar to those of the other leukemias and requires no special classification as to clinical behavior.

Clinical Findings. Most of the clinical histories and findings at physical examination were not different from those in the other forms of leukemia. The patients usually presented with such typical signs as chronic fatigue, weakness, weight loss, anorexia, lassitude, bone and joint pains, fever, sore throat, bleeding and purpura. On physical examination splenomegaly was present in almost all the patients when first seen, with an occasional exception [*26*]. Hepatomegaly was not as constant a feature at onset as was splenomegaly, but it was always present before the termination of the disease. Also, the expected physical findings of lymphadenopathy, bone tenderness, leukemic retinitis [*27*] or leukemia cutis [*27*] were present. Infiltrates into joints were extensive enough in one instance to cause joint deformities [*18,80*].

However, there were a few findings peculiar to this type of leukemia which occurred more frequently than is usual in other leukemias. The presenting signs and symptoms of a chronic productive cough, transient pulmonary infiltrations visible on chest roentgenograms, rales and cyanosis have been reported with striking frequency (45 per cent). Perhaps these pulmonary findings can be explained by the work of Vaughn [*81*] who found that even an induced eosinophilia caused widespread thickening of the alveolar walls with patchy consolidation in the lungs and eosinophil infiltrate in the hilar nodes and intestines. It seems likely, therefore, that the transient pulmonary manifestations seen early in the course, before true leukemic infiltration takes place, may be exclusively related to the eosinophilia.

Another peculiar reported finding was the frequent involvement of the cardiac musculature. Many patients had mural thrombi in both ventricles and the left auricle, or had areas of scarring or frank necrosis with eosinophilic infiltrate in the myocardium of the ventricles. This involvement was manifested clinically by systolic murmurs at the apex [*21,23*] and overt signs of failure such as tachycardia, anasarca and dependent edema. The involvement was so extensive in one patient that acute shock developed [*16*].

The patients also showed a high degree of predilection for manifestations of the central nervous system. These ranged from simple drowsiness to coma, convulsions, delirium or frank hemiplegia.

The patients whose course was acute presented with much more violent or specific complaints of fever, sore throat, headaches, bone pain and either signs of recurrent respiratory disease or neurologic involvement. Hepatosplenomegaly was usually present from the onset of symptoms. If respiratory signs or cardiac involvement were a prominent feature, there were usually cardiac murmurs and practically always pulmonary rales. When the neurologic complaints had been more prominent, some nerve paralysis with muscle weakness or frank hemiplegia was usually present. Convulsions were also frequent. Lymphadenopathy was usually absent or minimal.

Laboratory Findings. There has been only one reported case of aleukemic eosinophilic leukemia [*22*]. All the others presented with white cell counts of 19,000/cu. mm. or more. However, neither the degree of the leukocytosis nor the presence of entirely mature eosinophilic cells afford a differential point as to the acuteness or the chronicity of the disease. Only 30 per cent of the reported acceptable cases progressed with a chronic course although 55 per cent of the patients presented with hyperplasia of only the mature eosinophilis.

There have been reported cytologic findings said to be typical of eosinophilic leukemic cells. These were described as mature eosinophils with large granules staining both eosinophilic and basophilic, which tend to clump in certain areas of the cell leaving other areas of the cytoplasm relatively free of granules. There have also been reports of typical cells in the bone marrow of these patients [*18,80*]. These were described as large cells with a small, sharply defined, deeply stained nucleus with no nucleoli. The cytoplasm was light blue or did not stain at all and contained many minute bluish green granules or a few eosinophilic granules in the peripheral zone. (We did not observe any of these variations in our patient.) In addition, the eosinophils have been reported to be more motile [*56*] and more fragile [*24*]. The platelets were usually diminished throughout the disease.

X-ray examination showed transient pulmonary infiltrates in a high percentage of cases. These ranged from linear infiltrates throughout the lung fields [*27,30*] to large areas of consolidation [*22,26*]. These consolidations occurred in the apices in approximately 10 per cent of the

TABLE 1

ACUTE BLASTIC EOSINOPHILIC LEUKEMIA

Author, Year	Age (yr), Sex	Duration of Symptoms (mo.)	Clinical History and Physical Findings	Peripheral Blood*								Bone Marrow*						Necropsy Findings
				White Blood Count	Eosinophils (%)						Gm. %		Eosinophils (%)						
					Polymorphonuclears	Metamyelocytes	Myelocytes	Promyelocytes	Leukocytes	Blastocytes	Hemoglobin	Hemoglobin	Polymorphonuclears	Metamyelocytes	Myelocytes	Promyelocytes	Leukoblasts	Myeloblasts	
Stephens [16] 1935	17, F	3	Discoloration skin and fatigue 3 months, headache 10 days, fever and stupor 24 hr., pallor, purpura, cyanosis, coma, tachypnea, rales, blood pressure 0, lymphadenopathy right side of neck, no hepatosplenomegaly	130,000	67.6					16.6			0.2	1.0	0.9			98.6	Generalized petechiae, epicardial hemorrhages, mural thrombi and necrosis left ventricle, eosinophils and blast cell infiltrate in endocardium, spleen, liver and kidneys; occasional hyalinized glomerulus
Forkner et al. [17] 1937	33, M	1	Sore throat, anorexia and listlessness 1 mo., purpura, fever, drowsiness 15 days, stupor, nuchal rigidity, lymphadenopathy, cyanosis, leukemic retinitis, palate ulceration, hepatosplenomegaly, tachycardia	118,000 *265,000*	27 *29*	*0*	24 *24*	14 *11*	*0*	7.0 *5.0*	12.3	11.8							No postmortem
Thomsen, Plum [18,80] 1939	11, M	9	Sore throat, fever, large cervical nodes 3 mo., pallor, hepatosplenomegaly, ascites, recurrent attacks joint swelling and arthritis	42,000 *11,275*	62 *1*	8 *0*	4 *0*	*0*	*0*	*51*	10.3	3.4	19.5 *0.3*	10.5	1.5	12.5	0	42 *45.6*	Organized parietal thrombi in right auricle, right ventricle and left ventricle with underlying and surrounding fibrosis; blast infiltrate lymph nodes, lungs, spleen and liver
Astaldi, Curti [19] 1947	30, M	7	Fever, abdominal distention and discomfort, hepatosplenomegaly and lymphadenopathy	65,000 *165,000*	18 *9*	3.6 *0*	2.6 *0*	0.6 *1.5*		7.7 *67.5*			11.4 *14.2*	18.0 *9.4*	30.0 *15.0*	6.5 *8.0*	0 *0*	1.6 *19.4*	Myelogenous eosinophilic metaplasia of organs
Tolentino [20] 1948	8 F	4	Pain over bones, fevor, pallor, hepatosplenomegaly		*26*		41.0						1		1			96.5 *55.0*	No postmortem
Piney [21] 1949	18, F	1	Headache, lassitude, anorexia, ecchymoses on legs and feet, systolic murmur at apex. Sternum pain with pressure. Epistaxis	*67,000*	*17*		*31*	*23*					9		45			6	No postmortem
Hule [22] 1950	51, M	2	Anorexia, epigastric distress, hepatosplenomegaly	8,000	21.5 *17.5*	0.5 *2.0*		9 *12*		17 *34*	9.5							"Overrun"	No postmortem
Donohue et al. [23] 1950	7, M	"Alive"	Pain right knee 2 mo., fever 3 wk., enlarged cervical nodes, systolic murmur at apex, splenomegaly, cardiac failure on therapy	22,000	47						8.8		7.5	2.5	2.5			53	No postmortem
Kienitz, Burmeister [24] 1956	13, M	4	Easy fatigability, headaches, dyspnea, recurrent bronchitis, pallor, lymphadenopathy, fever, bone pain, bloody stools, splenomegaly	55,000 *66,000*	74 *57*					*2*	11	10.8	40 *11*	1	3			48 *83*	No postmortem

* Figures in roman represent presenting findings, figures in italics represent terminal findings.

TABLE II
MATURE CELL EOSINOPHILIC LEUKEMIA

Author, Year	Age (yr), Sex	Duration of Symptoms	Clinical History and Physical Findings	Peripheral Blood*								Bone Marrow*						Necropsy Findings
				White Blood Count	Eosinophils (%)						Gm. %		Eosinophils (%)						
					Polymorphonuclears	Metamyelocytes	Myelocytes	Promyelocytes	Leukocytes	Blastocytes	Hemoglobin	Hemoglobin	Polymorphonuclears	Metamyelocytes	Myelocytes	Promyelocytes	Leukoblasts	Myeloblasts	
Acute Course																			
Ham, Evans [25] 1929	41, M	3 wk.	Sore throat, enlarged tonsils with membrane, lymphadenopathy, splenomegaly, tachycardia, petechiae	72,187	75.5	4.4	3.8				9.5		*"Excess leukoblastic tissue—myeloblasts; eosinophil polymorphonuclears and myelocytes equal"*						Eosinophil leukemic infiltrate spleen, lymph nodes, liver, kidney and lungs
Hodgson et al. [26] 1945	44, F	3-4 mo.	Severe headache, diminution in vision, weakness right arm and leg, semicomatose on admission with cyanosis, flaccid right hemiplegia, bilateral VI nerve paralysis, papilledema, ulceration soft palate and rales	46,800	44.8								43.2 *51.5*	1.2 *13.5*	0.4 *13.5*	 *9.5*		 *7.0*	Pleural fluid, bilateral atelectasis, eosinophilic leukemic infiltrate into subpleural tissues, right dura, leptomeninges, pituitary region, choroid plexus, liver, spleen and liver
Norlander [27] 1951	44, M	10 mo.	Cough, weakness, anorexia, night sweats 2 mo., arthralgia, gingival bleeding, leukemic infiltrate skin and retina, paralysis V cranial nerve, hemiplegia, coma, hepatosplenomegaly	80,000 *348,000*	60 *43*	*20.5*	*1.0*			*0.5*	12.3	4.6	*"Many eosinophilic myeloblasts"*						Multiple hemorrhages in brain, largest into right internal capsule and ventricle; eosinophilic infiltrate left gasserian ganglion, liver, spleen, kidneys and lymph nodes
Piso [28] 1956	55, M	1 mo.	Ulceration palate, generalized ecchymoses, hepatosplenomegaly	84,000 *350,000*	84					*Present*			80 *Predominantly myeloblasts*					4	Blast cell and eosinophilic infiltrate in liver, spleen and lymph nodes; splenic infarcts; small areas of scar tissue myocardium
Engfeldt, Zetterstrom [29] 1956	8, M	?6 mo.	Attacks respiratory distress, easy fatigability, anorexia, pains in back of neck 3 mo., abdominal pain, vomiting and dyspnea, pallor, hepatosplenomegaly, tachycardia, episodes of cyanosis, pleural fluid, shotty cervical nodes	113,000	70								"Proliferation granulocytes; large percentage of myelocytes and segmented were eosinophils" *40*					*60 (undifferentiated cells)*	Hypertrophy both ventricles of heart with organized thrombus in right auricle and apex both ventricles; eosinophilic infiltrate in necrotic areas of heart, lungs, liver, spleen and kidney; occasional thrombosis vessel in kidney; end arterial "narrowing" of some small arteries in spleen and kidney

TABLE II (*Continued*)

MATURE CELL EOSINOPHILIC LEUKEMIA

Author, Year	Age (yr), Sex	Duration of Symptoms	Clinical History and Physical Findings	Peripheral Blood*									Bone Marrow*						Necropsy Findings
				White Blood Count	Eosinophils (%)						Gm. %		Eosinophils (%)						
					Polymorphonuclears	Metamyelocytes	Myelocytes	Promyelocytes	Leukocytes	Blastocytes	Hemoglobin	Hemoglobin	Polymorphonuclears	Metamyelocytes	Myelocytes	Promyelocytes	Leukoblasts	Myeloblasts	
Chronic Course																			
Harrison [30] 1930	23, M	1½ yr.	Cough, pain in chest, night sweats for 1½ yr.; hemoptysis 2 wk.; rales, hepatosplenomegaly	16,000 *13,450*	60 *50*	0	0	0	0	0	11.5	7.7	"*Hyperplastic-overwhelming majority eosinophils—mostly myelocytes, myeloblasts frequent*"						Pleural fluid, adhesions apex both lungs, mural thrombus left ventricle and small scars myocardium, spleen, liver and lymph nodes
Ravaul [31] 1942	60, M	8 yr.	Recurrent fever, jaundice and anemia 8 yr., hepatosplenomegaly, semicomatose	28,150 *70,500*	45 *64*	5 *1*	10 *4*	3 *5*	0	0 *3*	7.7	3.4	5.0	6.5	3.0	28	7.0	4.5	No postmortem
Rosa [32] 1949	30, M	39 mo.	Urticaria, pallor, dyspnea, congestive heart failure		28 *14*	4 *6*	0	0	0	0 *36*			7.4		46.5			3	Myocarditis, eosinophil infiltrate into lungs and kidneys
Evans, Nesbit [10] 1949	53, F	5 yr.	Urticarial skin nodules and recurrent bronchitis 5 yr.; lymphadenopathy, hepatosplenomegaly, tachycardia	19,000 *85,000*	20 *50*	0 *6*	0	0	0	0 *35*	7.9		30 *12*	*21*	15 *38*			2 *29*	Ulceration buccal mucosa, leukemic blast infiltrate epicardium, lungs, spleen, liver, adrenals, kidneys and lymph nodes
Hyman, Jarrold [33] 1952	34, M	3 yr.	Productive cough 3 yr.; weakness, weight loss, dyspnea, pallor 8 mo., anasarca 6 mo.; left hemiplegia, stupor, convulsions, papilledema	36,650 *175,730*	50 *66*	0 *0*	0 *0*	0 *0*	0 *0*	0 *5.5*	14	10	"35 to 45% eosinophils with many myelocytes" "*Sheets of eosinophilic myelocyte, metamyelocytes and polymorphonuclear cells*"						Pericardial fluid, hemorrhage into endocardium, perivascular eosinophilic infiltrate epicardium, eosinophilic infiltrate aorta, lungs, liver, leptomeninges, and choroid plexus, fibrosis spleen, lymph nodes and cerebrum
Morelli, Maurea [34] 1953	47, M	23 mo.	Easy fatigability, pallor, weakness, hepatosplenomegaly	19,500 *76,400*	72	7	4	1					*40.5*	*0.5*	*4.5*			*53*	No postmortem

* Figures in roman represent presenting findings, figure in italics represent terminal findings.

† The author does not classify this patient as having leukemia. Yet by our definition it seems to fit in this category.

patients and could conceivably be confused with tuberculosis. In a few instances survey of the long bones showed the metaphyseal translucency seen in other forms of leukemia [*23*]. Cardiomegaly was a prominent feature in the patients with cardiac involvement. The electrocardiogram frequently showed T wave changes, prolonged P-R intervals or widened QRS complexes, indicating the oft demonstrated cardiac involvement [*18,80*].

Pathology. The pericardium occasionally contained fluid [*30,33*] and was sometimes thickened as a result of leukemic infiltrate [*33*]. If affected, the heart was enlarged, with ventricular hypertrophy and gray streaking of the myocardium. The epicardium in some instances contained small hemorrhages or frank leukemic infiltrate [*10,33*]. Approximately 20 per cent of the reported patients had a mural thrombus of the left ventricle but this also occurred in the right auricle and/or ventricle. Frequently there were areas of necrosis in the myocardium, with intense infiltration of eosinophils in this area while other areas sometimes showed minute areas of scarring or inflammatory changes with infiltration of eosinophils. The endocardium was involved in all degrees of severity from thickening of the valve edges [*12*] to gross thickening of the entire endocardium due to leukemic infiltration [*16*].

There was fluid in the pleural cavity in a few instances [*26,30*] but no adhesions were reported. Atelectasis of entire lobes of the lung has been described. Small necrotic areas of lung parenchyma were seen and were usually secondary to infiltrates [*10,25,29,33*]. On microscopic examination there was interstitial or peribronchiolar infiltrate with eosinophils or myeloblasts and in the majority of cases the alveoli were filled with exudate and eosinophils.

The spleen was almost invariably enlarged. There were several instances of splenic infarct or patches of necrosis [*28,29*]. On microscopic examination the follicles were usually obscured by leukemic cells and the sinusoids packed with eosinophils or myeloblasts. The liver was usually enlarged as a result of infiltration of eosinophils and/or myeloblasts in the sinuses and portal areas. Occasionally fibrosis of the portal tracts was also present. On the lymph glands there was usually leukemic infiltration in the sinuses and the follicles to such an extent that the architecture was destroyed. The kidneys occasionally exhibited infiltration of the interstitial areas with parenchymatous degeneration of the tubules. Stephen's patient [*16*] had hyalinized glomeruli which, of course, may not have been related to the leukemia.

Infiltration of the meninges was the most frequent finding of the central nervous system. These sometimes caused quite large tumors with resultant compression of the brain tissue. Hemorrhages into the brain substance were seen, which at times progressed to large hemorrhages into the ventricle [*16,27*].

Infiltrates were also seen in the adrenals, testes, skin and larynx.

Differential Diagnosis. In the early stages of this disease one is confronted with a patient who has a high white blood cell count and an extreme eosinophilia without immature cells. The diagnosis here must be made by exclusion [*82,83*] as there are so many diseases which give a similar leukemoid picture.

Periarteritis nodosa may present with a clinical picture indistinguishable from eosinophilic leukemia. The white blood cell count may be as high as 65,000/cu. mm. with 75 per cent eosinophils [*84*]. The cells are chiefly adult but the marrow may show a high percentage of eosinophil myelocytes [*85*]. A biopsy of organs may be confusing because of massive eosinophil infiltration into the spleen, the lymph nodes and the periportal areas of the liver [*85,86*]. However, the typical perivascular changes make the diagnosis clear.

When asthma occurs with a leukocytosis and hypereosinophilia of this type, it is often associated with periarteritis nodosa [*87–89*]. These patients may have heart failure due to myocardial eosinophil infiltration or mural thrombus [*90*], purpura [*90,91*], eosinophilic lung infiltration with cyanosis [*92*] and edema of the legs [*93*].

Loeffler's syndrome is usually easily distinguished by the clinical differences and an eosinophilia not exceeding 35 per cent [*94*].

Hodgkin's disease can cause a leukocytosis in the range of 170,000/cu. mm. with 98 to 99 per cent eosinophils [*7*]. However, the eosinophilia is present only when the white blood cell count is elevated [*8*].

Acute parietal endocarditis with eosinophilia may be a stumbling block in diagnosis. The patients may present in heart failure with edema, hepatosplenomegaly and marked eosinophilia [*95*]. On postmortem examination there is endocardial fibrosis and extensive mural thrombus of one or both ventricles as seen in eosino-

philic leukemia. However, the leukemic changes are not present.

Patients with allergic granuloma of the lung rarely have eosinophilia over 10 per cent [*96*] and the clinical picture is that solely of respiratory symptoms.

Patients with myelogenous leukemia may present with a picture of eosinophilic leukemia or during the course of the disease develop a picture indistinguishable from eosinophilic leukemia [*5,6*]. Also, it is not uncommon to have eosinophilic infiltrate in lymph nodes in granulocytic leukemia, and eosinophils in significant number in the bone marrow of the Naegeli type monocytic leukemia or granulocytic leukemia [*97*]. However, these episodes are transient and do not persist as in eosinophilic leukemia.

Infiltrative eosinophilia secondary to parasitic infections may occur, with a leukocytosis of 100,000/cu. mm., 60 per cent of the marrow elements being mature eosinophils [*98*]. This can be due to several parasites that support hypersensitivity, such as Ascaris lumbricoides, Schistosoma mansoni, Filaria bancrofti, Fasciola hepatica, Endamoeba histolytica, Necator americanus, Strongyloides stercoralis and Trichinella spiralis [*98,99*]. In children one of the most common causes of such extreme eosinophilia is visceral larva migrans due to Toxicara cana [*100–102*]. This is characterized by hepatomegaly, eosinophilia and hyperglobulinemia in the typical cases [*100*]. There may, however, be involvement of the eyes, central nervous system or lungs so that the clinical picture is indistinguishable from eosinophilic leukemia [*101*]. The bone marrow shows extreme eosinophilia, with eosinophils in all stages of development. A biopsy of the involved organ is necessary to reveal the offending larva as it is not found in the stool. The pathologic findings are fairly typical and are thought to be the cause of the eosinophilia reported by Zuelzer and Apt [*103*]. An identical clinical picture is also present in children infested with Capillaria hepatica and only a liver biopsy serves to distinguish the two [*104*].

Various carcinomas have caused eosinophilia of enormous proportions. This has been reported in carcinoma of the cervix [*1*], colon [*2*], lung [*3*] and stomach [*4*]. Miliary tuberculosis has been implicated as causing an eosinophilic leukemoid picture [*105,106*]. However, in the case report of Brumlik [*105*] it is difficult to distinguish whether or not the miliary tuberculosis was superimposed on an eosinophilic leukemia. Lesions of the skin have been reported to cause eosinophilia. Sibley [*107*] described a patient with lymphadenoma of the skin with an eosinophilia of 39.6 per cent. Likewise Dermatitis herpetiformis causes a striking eosinophilia [*106,108,109*]. Acute colitis has been reported to cause a leukocytosis of 42,000 cu. mm. with a marked eosinophilia of the bone marrow [*110*]. Massive eosinophilic infiltration of the intestines with a peripheral blood eosinophilia has been reported with no obvious etiology. This can be extensive enough to cause obstruction [*111*].

Familial eosinophilia has been reported several times [*112,113*]. The eosinophilia is never severe enough to confuse it with eosinophilic leukemia.

Streptococcal infections may cause an eosinophilia but rarely over 5 to 8 per cent although it sometimes may rise as high as 17 per cent [*114*]. Other causes of eosinophilia which should not cause diagnostic difficulties are chorea [*115*], erythema multiforme [*14*], gonorrhea [*14*] and leprosy [*116*].

Treatment. As in all forms of leukemia, therapy is unsatisfactory. Several agents have been used with varying results. In only a few of the reported cases was a good clinical remission ever achieved.

ACTH and cortisone have been given to seven patients, including the present one. An acceptable remission was obtained in four of these, three deriving no benefit at all. Nitrogen mustard has been used in two cases, with a remission in both. Urethane was used twice, with an acceptable remission in one instance and a partial remission in one. Myleran was used in our patient, with a brief hematologic response. Six-mercaptopurine was given with no beneficial results.

SUMMARY

A patient with eosinophilic leukemia is described. Twenty acceptable cases of eosinophilic leukemia from the literature are reviewed.

The diagnosis of eosinophilic leukemia cannot be definitely established unless there is an abnormal number of immature cells in the blood and tissues. When one is confronted with a patient who has an extreme eosinophilia consisting only of mature cells the diagnosis must be one of exclusion.

The clinical, physical, laboratory and patho-

logic findings in eosinophilic leukemia are reviewed.

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An Abnormality of Thyroid Hormone Secretion*

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IT is now well established that thyroxine is the principal labeled thyroid hormone which can be recovered from the serums of patients given radioactive iodine, even when large doses of radioactive material are employed [*1*]. The occurrence of small quantities of triiodothyronine in human serum was first described by Gross and Pitt-Rivers [*2*]. In a similar study Benua et al. [*3*] found that when circulating I^{131} labeled triiodothyronine was present, its concentration was greater than thyroxine only in the very early period following I^{131} therapy.

The purpose of this communication is to report the unusual finding of large quantities of triiodothyronine in the serum of a patient with thyroid carcinoma. This was demonstrated following the administration of three successive therapeutic doses of radioactive iodine.

CASE REPORT

A forty-eight year old man was transferred to the St. Louis Veterans Administration Hospital in April 1955 with the diagnosis of a tumor of the fourth lumbar vertebra. On physical examination a small nodule was noted in the isthmus of the thyroid gland. There was tenderness over the spine of the fourth lumbar vertebra. The basal metabolic rate was plus 48. Roentgenographic examination of the lumbosacral spine revealed the presence of an osteolytic process involving the body and lamina of the fourth lumbar vertebra. In May 1955 a left hemithyroidectomy was performed with the pathologic diagnosis of well differentiated carcinoma of the thyroid gland. This was followed by a total thyroidectomy. Postoperatively, radioiodine studies revealed concentration of the radioactive material in the lumbar area and three 25 mc. doses of I^{131} were administered over a period of several weeks.

In November 1955 progressive spastic paralysis of the lower extremities developed in the patient which necessitated readmission to the St. Louis Veterans Administration Hospital. His basal metabolic rate was plus 72, later plus 38. The serum protein-bound iodine was 3.4 μg. per cent. Roentgen therapy to the lower part of his back as well as 75 mc. of I^{131} were administered without symptomatic relief. In January 1956 a decompression laminectomy was performed, and thyroid carcinoma was found in the excised fragments. Postoperatively the paraplegia regressed.

On readmission to the hospital in November 1956, the only physical finding was a wasting away of the muscles of the lower extremities. There was no clinical evidence of hypothyroidism. The protein-bound iodine was 4.1 μg. per cent. Following the administration of a tracer dose of I^{131} the conversion ratio was 82 per cent. A scintigram of the neck region failed to demonstrate the presence of any radioactivity in the thyroid area. Scanning over the back revealed two concentrations of the radioactive material, one at the level of the second thoracic vertebra and another over the fourth lumbar vetebra. One hundred and five millicuries of I^{131} were administered in November 1956, blood was obtained forty-eight hours later for the study of labeled thyroid hormone content.

The patient was again admitted to the hospital in September 1957 after suffering a fracture of the neck of the left humerus in a fall. Physical findings were limited to pain and tenderness in the lumbar area and also at the fracture site. A roentgenogram of the left shoulder revealed the presence of a fracture of the neck of the humerus. There was nothing to suggest that this was a pathologic fracture. Tracer studies again demonstrated the concentrations of radioactive iodine in the same locations as on the previous hospital admission, but none at the fracture site. In September 1957, 130 mc. of I^{131} were administered and blood was obtained at twenty-four, forty-eight and seventy-two hour intervals for analysis of labeled hormone.

The most recent admission to the St. Louis Veterans Administration Hospital was in June 1959 with the complaint of progressive loss of strength in the lower extremities. These changes were noticed about three months prior to this admission. The patient had not taken thyroid extract as had been recommended in

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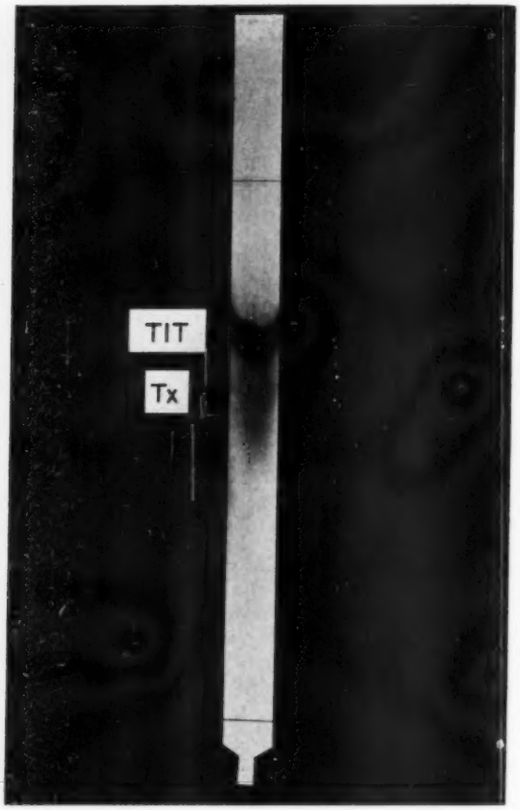


FIG. 1. A radioautograph of the chromatogram of serum obtained forty-eight hours after I^{131} therapy. Tx refers to carrier thyroxine and TIT to triiodothyronine.

September 1957. Serum protein-bound iodine was 4.1 μg. per cent. Following the administration of a tracer dose of I^{131}, the conversion ratio at forty-eight hours was 60 per cent. Scanning revealed two areas of radioactivity in the spine identical in location with those previously described. A 110 mc. dose of I^{131} was administered, serum being obtained twenty-four, forty-eight and seventy-two hours afterward for chromatographic analysis. Thyroid extract therapy was instituted several days later and the patient was discharged with instructions to return for re-evaluation in six weeks.

METHODS OF STUDY

For the chromatographic studies carried out during the 1956 and 1957 hospital admissions the patient's serum was precipitated with trichloracetic acid and the precipitate extracted with butanol. The extracts were concentrated under vacuum and aliquots of each were chromatographed by the ascending method on Whatman No. 1 paper cut in tapered form [*4*]. The following two solvent systems were employed: (1) butanol-dioxane-ammonia [*5*], and (2) butanol-acetic acid-water [*6*]. Radioactivity on the strips was located by radioautography on no-screen x-ray film and by scanning with an automatic scintillation counter.

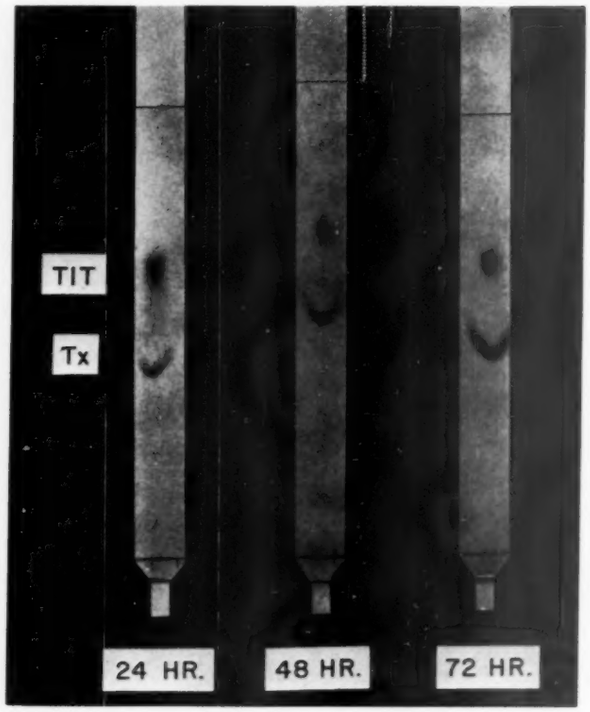


FIG. 2. Radioautographs of chromatograms of serum obtained twenty-four, forty-eight and seventy-two hours after the second therapeutic dose of I^{131} with the position of carriers indicated.

Thyroxine, triiodothyronine,* iodide and diiodotyrosine were similarly chromatographed with each aliquot of plasma extract. Spraying the strips with ninhydrin revealed the location of the former two. Iodide and diiodotyrosine were detected by spraying with ceric sulfate-arsenious acid reagent.

The serum collected during the most recent hospital admission was acidified, extracted with butanol saturated with 0.1N HCl and the extract concentrated under vacuum. Chromatography of filter paper strips was carried out as before in butanol-dioxane-ammonia. Radioactivity and carrier thyroxine and triiodothyronine were located as already described. Two-dimensional chromatograms were also obtained for each serum sample using butanol-dioxane-ammonia followed by butanol-ammonia [*7*]. The location of radioactivity was compared to that of carrier thyroxine and triiodothyronine.

RESULTS

The chromatograms of the patient's serum in the butanol-acetic acid-water system failed to disclose either mono- or diiodotyrosine. Figure 1 depicts the radioautograph of a chromatogram of the patient's serum obtained in November

* The L-thyroxine and L-triiodothyronine used in this study were made available to us through the kindness of H. A. Klusek of Smith, Kline and French Laboratories, Philadelphia, Pennsylvania.

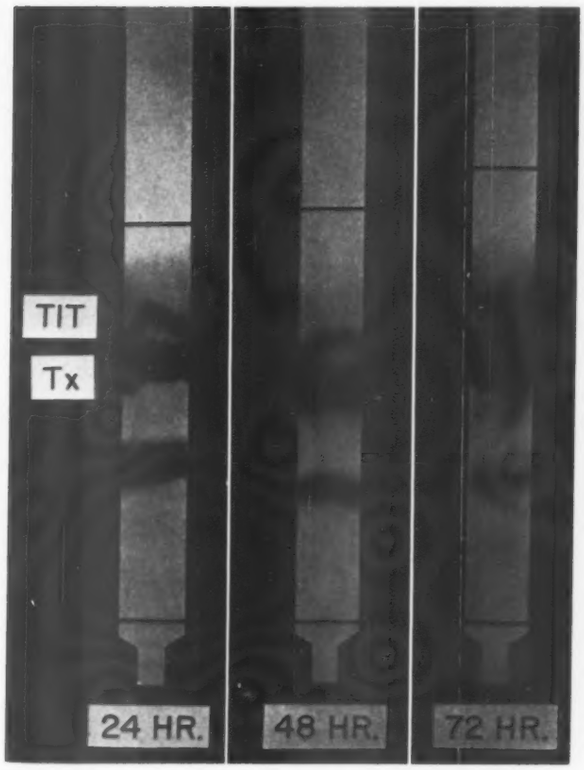


FIG. 3. Radioautograph of the patient's serum obtained after the most recent therapeutic dose of radioiodine. Most of the radioactivity is associated with thyroxine.

1956, forty-eight hours after radioiodine therapy. The location of the carrier thyroxine and triiodothyronine on the chromatogram is indicated by the markers. Although separation is not complete, most of the radioactivity is at a level corresponding to triiodothyronine. Analysis of this chromatogram by means of an automatic scanning counter demonstrated approximately 80 per cent of the total radioactivity associated with triiodothyronine. In Figure 2 are the radioautographs of chromatograms obtained following a second therapeutic dose of radioiodine ten months later. The strips represent samples of blood drawn at twenty-four, forty-eight and seventy-two hours. The concentrations of radioactivity at the level of thyroxine and of triiodothyronine appear approximately equal in each of the strips. In Figure 3 are radioautographs of chromatograms obtained following the most recent therapeutic dose. Two bands of radioactivity are seen which correspond to the thyroxine and triiodothyronine labels. The two-dimensional chromatogram in Figure 4 clearly demonstrates thyroxine, triiodothyronine and iodide.

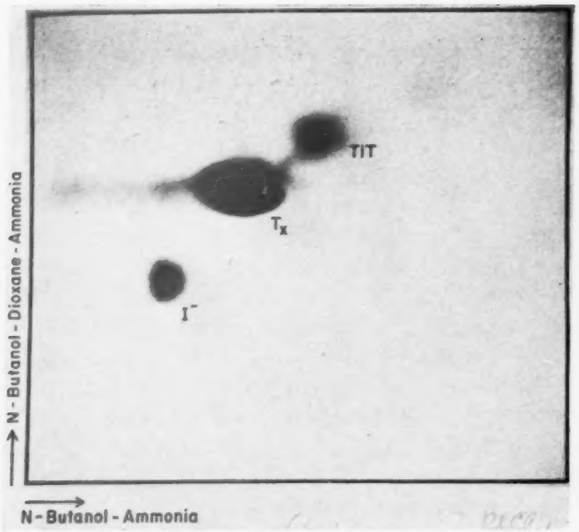


FIG. 4. A two-dimensional chromatogram of the patient's serum forty-eight hours after the last time I^{131} therapy was given. Triiodothyronine is well separated from thyroxine.

COMMENTS

This patient is of particular interest in that a euthyroid state has continued more than four years following total thyroidectomy. The finding of an elevated I^{131} conversion ratio on two occasions is in marked contrast with the normal serum protein-bound iodine determinations. A somewhat analogous situation may be found in the low serum protein-bound iodine level of myxedematous patients maintained in a euthyroid state by triiodothyronine [*8,9*].

Other investigators [*10,11*] have noted artifacts with trichloracetic acid precipitated serum and in butanol-containing chromatographic systems, both of which were employed in the first two studies of this patient. Such artifacts have been shown to appear ahead of thyroxine, where one might expect to find triiodothyronine.

The occurrence of a predominant radioactive serum component corresponding to triiodothyronine has been noted in three of nineteen patients studied in a similar fashion in our laboratory. In addition to the case reported herein, both of the other patients had had a total thyroidectomy for thyroid carcinoma and were receiving therapeutic I^{131} to eradicate residual thyroid tissue. The infrequent finding of this quantitatively abnormal serum component in our series of patients argues against its being an artifact. In view of the clear identification of triiodothyronine on the more recently obtained two-dimensional chromatogram, it is

reasonable to conclude that this patient's metastatic lesions have persistently secreted large quantities of triiodothyronine.

The explanation for the abnormal secretion of triiodothyronine in our patient is obscure. Increased quantities of it have been found in the serums of hyperthyroid patients and in euthyroid persons following the administration of thyroid-stimulating hormone [*12,13*]. Rupp and his associates [*14*] have recently noted the occurrence of triiodothyronine as the only circulating thyroid hormone in a patient with a non-toxic goiter. They postulate an intrathyroidal enzyme defect leading either to the almost exclusive production or secretion of triiodothyronine. Since their patient also demonstrated an elevated I^{131} conversion ratio, a qualitatively similar enzymatic defect may exist in our patient.

Inspection of the one-dimensional chromatograms demonstrates a progressive decrease in triiodothyronine and a corresponding increase of thyroxine with the administration of each therapeutic dose of I^{131}. It is interesting to speculate that this change may represent an effect of radiation on the metastatic cells resulting in an anatomically and functionally more mature lesion.

SUMMARY

A patient with thyroid carcinoma whose metastatic lesions have been demonstrated to secrete abnormally large amounts of triiodothyronine is described. It is suggested that this quantitative abnormality may result from an intracellular enzymatic defect in the metastasis.

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Thyroid Function and Periodic Paralysis*

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NUMEROUS etiologic factors may lead to the syndrome of hypokalemic periodic paralysis. The majority of cases are familial [*1*]. Sporadic occurrences with primary hyperaldosteronism have been reported [*2–4*], as have rare but well proved cases of potassium-losing nephritis [*5–7*], renal tubular acidosis and Fanconi's syndrome [*8,9*], bilateral ureterosigmoidostomies [*10*], in the recovery phase of diabetic acidosis [*11*], and following chlorothiazide [*12*] or p-aminosalicylic acid therapy [*13,14*]. Most of the sporadic cases, however, are instances of thyrotoxic periodic paralysis [*15*].

The distribution of cases of periodic paralysis according to cause is difficult to estimate. Of the cases reviewed by Talbott in 1941 80 per cent were familial [*1*]. Most patients in his report were of European or American origin. In Japan the thyrotoxic cases are far more prevalent than the familial ones [*15–17*]. In less than the three-year interval following the first case described in association with hyperaldosteronism, thirteen additional cases have been reported [*3*].

The pathophysiologic mechanisms underlying periodic paralysis are diverse [*18*]. Hypokalemia caused by potassium wastage is a common feature of sporadic cases associated with renal disease or adrenal tumors. In thyrotoxic and in familial periodic paralysis potassium retention by the kidneys preceding and during paralytic attacks is commonly seen [*19*]. However, in some familial cases there may be no hypokalemia at the height of the attacks [*20*].

The thyrotoxic and the familial forms of periodic paralysis differ in several respects. Excluding cases mentioned in more than one report, 228 case reports of thyrotoxic periodic paralysis were found in the literature to date [*15–17,21–40*]; 205 of these have been reported from Japan. Sex was specified in 212 cases; of these 184 were males and 28 were females, giving a male:female ratio higher than 6:1. The sequence of onset of the two disorders could be ascertained in 138 cases. In 113 of these (82 per cent), the thyrotoxicosis preceded or appeared simultaneously with the periodic paralysis. The age of onset of the periodic paralysis was specified in 143 instances. In only twelve of these (8 per cent), did paralytic attacks appear before the nineteenth year of life; in 120 patients (84 per cent), the attacks began between the ages of twenty and thirty-nine. A positive family history for periodic paralysis was reported in only five cases (2 per cent) [*15,23,29,30,36*]. In three of these five cases the affected relative was also thyrotoxic. The results of antithyroid therapy are mentioned for 159 patients. The thyrotoxicosis is described as cured in 152 patients and as alleviated in seven others; the periodic paralysis is described as completely relieved in 141 patients and improved in ten others.

In contrast, in the cases of familial periodic paralysis reviewed by Talbott [*1*] more than 60 per cent began before the sixteenth year of life, and the male:female ratio was 3:1; the thyrotoxic cases mentioned in this review were all sporadic.

The adverse effects of thyroid medication on thyrotoxic periodic paralysis were described by Shinosaki in 1926 [*23*] and by Robertson in 1954 [*37*]. Of the seven patients without familial periodic paralysis treated by Shinosaki four had goiters but only one of these was described as toxic. In all seven patients the paralytic attacks became more frequent and severe on a dosage 0.3 to 0.5 gm. of thyroid extract per day, seven to twenty-five days after the start of therapy. Seven patients with the familial form of the disease were treated with thyroid extract by Wolf [*41*]. According to this investigator, impending paralytic attacks could be regularly aborted by the administration of 3 gr. of thyroid extract. One patient became so enthusiastic that he took too much thyroid substance and became toxic. He became progressively weaker

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only following the withdrawal of thyroid medication.

These differences seem to indicate that the latent abnormality for periodic paralysis in the thyrotoxic cases may not be the same as the abnormality in the familial form of the disease. The objective of this study was to evaluate further the difference between these two forms of the disease by means of thyroid function studies carried out in a patient with familial periodic paralysis.

The patient under study was a twenty-six year old white man who had had periodic attacks of paralysis since the fourth year of life. These were precipitated by sleep, the ingestion of high carbohydrate meals or by exposure to cold. The family history was positive for periodic paralysis. The father, one sister and one brother among six siblings had attacks similar to those of the patient; another sister had migraine headaches. While under observation the patient regularly became weak four hours after going to sleep and remained weak until morning. Quadriceps muscle biopsies carried out before and during attacks showed the incompletely reversible vacuolar myopathy which is characteristic of the disease [*42,44*]. The serum potassium levels in attacks varied between 2.5 and 3.8 mEq. per L. Oliguria preceding and during paralysis, followed by increasing urinary output during recovery, were always noted. The adverse effects of sodium loading and the protective effects of sodium depletion have been described in this patient by Rowley and Kliman [*43*]. The same investigators found no evidence for a primary disturbance of aldosterone metabolism in this case.

Throughout the study the patient was on a 2,000 calorie diet consisting of 250 gm. carbohydrate, 70 gm. protein and 80 gm. fat. The daily dietary sodium and potassium intakes were each held constant at 140 mEq. An additional 302 mEq. of potassium was administered as 30 ml. of a 25 per cent potassium chloride solution at 3 A.M., 5 P.M. and 10 P.M. Additional doses of potassium chloride were given only on six occasions during the study, for quadriplegic attacks in the daytime.

The patient's clinical status was evaluated five times daily, once before each dose of potassium chloride, as well as at 8 A.M. and at 12 noon. The evaluation consisted of the following: (1) The hand grip was measured five times daily on a calibrated spring dynamometer, in pounds. If less than 10 pounds, it was measured in millimeters of mercury on a sphygmomanometer with its cuff wrapped around a 4 inch cylinder. The mean of the right and left grip was taken as the reading. (2) Manual muscle testing of four predetermined pairs of muscles, graded according to the Poliomyelitis Foundation scale from 0 to 5, was carried out daily at 8 A.M. (3) The ability to lift the head, turn over in bed, sit up or stand up were observed at 3 A.M. and at 8 A.M., and whenever quadriparesis supervened. The vital capacity was determined whenever the patient was unable to sit up.

Thyroid function was evaluated by daily measurements of the basal metabolic rate, resting pulse and body weight; weekly measurements of serum protein-bound iodine, twenty-four–hour radioiodine uptake and serum cholesterol. The basal metabolic rate was measured by the closed method on a Sanborn Metabulator. With careful attention to basal conditions and the elimination of oxygen leakage, the metabolic rate fluctuated less than 2 per cent when the patient was metabolically stable.

The daily urinary excretions of potassium, sodium and chloride were measured during the entire study on specimens collected from 8 A.M. to 8 A.M. of the following day. The serum potassium, sodium and the fasting blood sugar were determined five times weekly in blood specimens drawn at 8 A.M.

For an initial period of fourteen days, baseline observations were obtained on the patient's metabolic and clinical status. The steps in the subsequent study were as follows: (1) l-Triiodothyronine was administered at the dose level of 100 μg. for ten days. Effective inhibition of pituitary thyrotropin secretion without hypermetabolism could be expected at this dose level [*45–49*]. (2) l-Triiodothyronine was next administered in progressively higher doses for the next twenty-five days. The length of this period was determined by the patient's tolerance to hypermetabolism. (3) After an interval of twenty-one days, thyrotropin (Armour) (TSH) was administered in graded doses for twenty days.

The first and second steps were designed to study the effects on the periodic paralysis of the inhibition of endogenous pituitary thyrotropin secretion, first without and then with concurrent hypermetabolism. The third step differed from the second one in that hypermetabolism was induced by exogenous thyrotropin through activation of its endocrine target, the thyroid gland.

Initial Observations. During the initial control period the patient appeared weakest at 3 A.M. He could usually turn over in bed, but could sit up only with difficulty. The hand grip at this hour varied between 10 and 14 pounds. The vital capacity was reduced 35 to 55 per cent below the expected normal value. By 8 A.M. the patient became stronger; he could sit up with ease and his hand grip varied between 20 and 30 pounds. During the rest of the day he gradually gained strength, the hand grip attaining 50 to 65 pounds by 5 P.M. Quadriparesis did not occur in the daytime. The basal metabolic rate ranged between minus 7 and minus 9 per cent; the serum protein-bound iodine was 4.9 μg. per cent and

the twenty-four–hour radioiodine uptake was 12.5 per cent. The mean urinary excretion of sodium and potassium was 27 and 53 mEq. less than the respective dietary intakes. The 8 A.M. serum potassium values varied between 4.9 and 5.3 mEq. per L.

Effects of l-Triiodothyronine at a Dose Level of 100 μg. per Day (Fig. 1). The twenty-four–hour radioiodine uptake fell to 2.7 per cent, indicating suppression of endogenous thyrotropin secretion. The serum protein-bound iodine became slightly depressed, to 3.2 μg. per cent. The basal metabolic rate remained stable.

No significant changes in the periodic paralysis could be seen, either at 3 A.M. when the patient's weakness was maximal or subsequently during the day. Urinary and serum electrolyte values did not deviate appreciably from previous values.

Effects of Progressively Higher Doses of l-Triiodothyronine. During this period the twenty-four–hour radioiodine uptake fell to 0 per cent and the serum protein-bound iodine gradually declined to 2.6 μg. per cent. The basal metabolic rate rose gradually to plus 31 per cent as the daily dose of triiodothyronine was upgraded to 1,050 μg.

The effects on the manifestations of periodic paralysis were not impressive. The general strength at 3 A.M. and 8 A.M. declined slightly, the 8 A.M. grip now ranging from 18 to 22 pounds. One daytime paralytic attack occurred four days before the termination of triiodothyronine therapy. The daily urinary excretion of potassium fell appreciably under preceding values only on four of the twenty-five days of this period. The daily excretion of sodium did not change significantly. The 8 A.M. serum potassium values remained within the normal range.

Effects of l-Triiodothyronine Withdrawal. The metabolic rate returned to baseline values seven days after the administration of l-triiodothyronine was discontinued. The twenty-four–hour radioiodine uptake rebounded to 23 per cent in fifteen days. The serum protein-bound iodine rose to 4.1 μg. per cent seventeen days after l-triiodothyronine withdrawal.

Concurrently with the decline of the basal metabolic rate, the periodic paralysis became worse. Quadriplegia and loss of the hand grip were seen at 3 A.M. eight days after l-triiodothyronine withdrawal; the 8 A.M. grip was completely lost three days later and the patient could sit up in bed only with difficulty even at that hour. Five quadriplegic attacks also occurred in the daytime after the basal metabolic rate returned to normal. The serum potassium rose from 5.8 to 6.2 mEq. per L. during this period. Thus the decline in strength was not associated with a depression of serum potassium values. Pronounced reduction in daily urinary excretion of potassium was noted on five occasions. Changes in urinary excretion of sodium did not precede or consistently parallel the changes in excretion of potassium.

Effects of Graded Doses of Thyrotropin. The basal metabolic rate rose forty-eight hours after thyrotropin administration was begun. As thyrotropin dosages were upgraded from 7.5 to 30 units per day, the metabolic rate became elevated to plus 25 per cent. The high radioiodine uptake (52 per cent) and a gradual elevation of the serum protein-bound iodine to 10.4 μg. per cent during this period were in keeping with the increased activity of the thyroid gland under the influence of thyrotropin.

On this therapy the periodic paralysis improved rapidly and the previous loss of strength disappeared in five days. The clinical status then remained stable at pre-study values for the remaining part of the thyrotropin therapy. With the return of strength the 8 A.M. serum potassium values fell again to between 5.5 and 6 mEq. per L. The urinary excretion of potassium decreased during the last three days of thyrotropin therapy. Day to day variations in sodium excretion appeared to be random.

Effects of Thyrotropin Withdrawal. The metabolic rate returned to baseline values twelve days after the cessation of thyrotropin therapy and then fell further to minus 14 per cent. The serum protein-bound iodine declined to 3.2 μg. per cent nineteen days after thyrotropin withdrawal. Depression of the basal metabolic rate and of the serum protein-bound iodine below baseline values was attributed to the depression of the thyroidal secretion rate below the baseline following the withdrawal of thyrotropin [*50*].

With the falling off of the metabolic rate the periodic paralysis again became worse, the decline in all parameters of strength paralleling the decline in the metabolic rate. Quadriplegia and weakening of hand grip appeared seven days after thyrotropin withdrawal; the 8 A.M. grip was lost three days later. Quadriplegic attacks again appeared in the daytime and between attacks the patient's legs remained weak. A very slow and gradual reduction in the

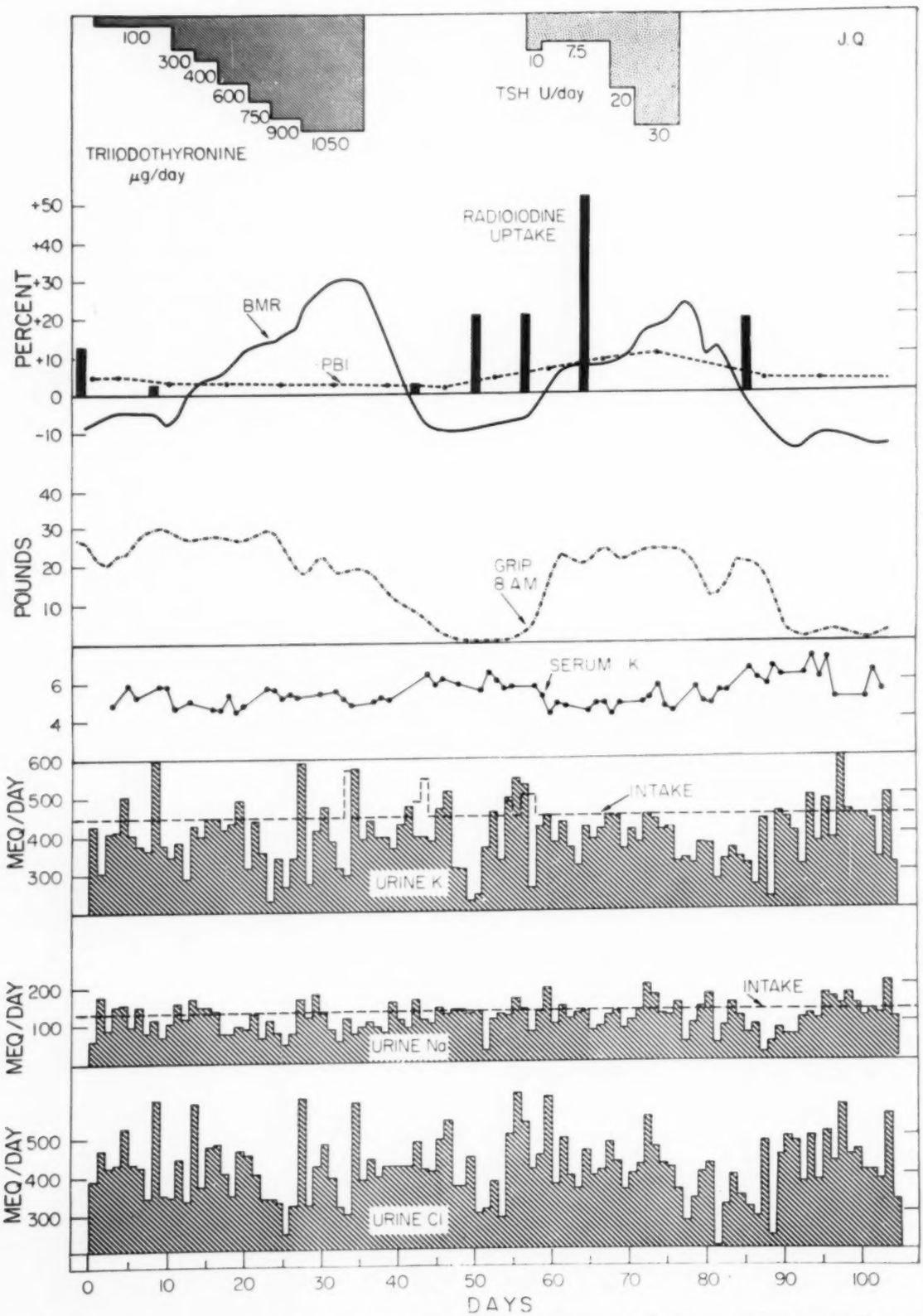


FIG. 1. The effects of graded doses of l-triiodothyronine and thyrotropin. The basal metabolic rate (BMR) and grip lines consist of daily values plotted as three-day moving averages. Protein-bound iodine (PBI) values indicate micrograms per cent. Serum potassium values are in milliequivalents per liter.

severity of the nocturnal paralysis and an improvement of daytime strength occurred over the subsequent twenty-five days. Serum potassium values again rose to 6 to 6.2 mEq. per L. The daily excretion of sodium and potassium decreased while the basal metabolic rate was falling, but rose again to the values before study as the exacerbation of the periodic paralysis became apparent.

COMMENTS

Hypermetabolism, first induced by the administration of l-triiodothyronine and then by thyrotropin, had no immediate adverse effects on the periodic paralysis. Delayed exacerbations occurred twice, each time with return of the basal metabolic rate to normal values. The first exacerbation following l-triiodothyronine withdrawal was promptly relieved by thyrotropin administration.

Inhibition of endogenous thyrotropin secretion in the absence of hypermetabolism had no effect on the periodic paralysis. The rebounding phase of pituitary thyrotropin secretion coincided with the first exacerbation. As the patient's condition was improved by exogenous thyrotropin therapy instituted at this time, thyroid rather than pituitary thyrotropin secretion determined the effects on the periodic paralysis.

Hypokalemia was not a feature of the two exacerbations. Although normokalemic familial periodic paralysis has been described [*20*], this is of interest because spontaneous or glucose-induced attacks in this patient were previously regularly associated with depression of the serum potassium.

Decreased urinary excretion of potassium during the first exacerbation, and of potassium and sodium before the second exacerbation, was noted. Diurnal fluctuations in electrolyte excretion could not be estimated because urine collections were pooled over twenty-four hours.

Thyroid hormones may affect periodic paralysis by enhancing urinary excretion of sodium and potassium [*51*] and by promoting the ingress of potassium into red blood cells [*52*]. However, in this study there was no urinary sodium or potassium wastage during l-triiodothyronine or thyrotropin administration. Erythrocyte potassium concentrations were not determined, but even if a potassium shift into red cells had occurred during the induced thyrotoxicosis this would not explain the onset of the weakness after withdrawal of thyroid hormone.

Another mechanism of thyroid hormone action on periodic paralysis could be mediated by the adrenal gland. Adrenal cortical hyperplasia has been observed in thyroxinized rats and mice [*53*]. If an oversecretion of either aldosterone or of glucocorticoids would have persisted after withdrawal of thyroid hormone, increased weakness might have been noted at that time. This still does not explain why the increased weakness did not appear before the withdrawal of thyroid hormone. Also, if the two exacerbations had been caused by simultaneous hyperaldosteronism, they should have been associated with urinary potassium wastage, sodium retention and hypokalemia [*2*]; these were not seen. It is also unlikely that the postulated hyperaldosteronism would have remitted promptly upon administration of thyrotropin.

The effect of thyrotoxicosis on the familial periodic paralysis in this patient was different from that seen in the non-familial, thyrotoxicosis-conditioned form of periodic paralysis. In the latter disease the immediate adverse effects of thyroid extract and the monotonously curative effects of antithyroid therapy indicate a direct aggravating effect on the disease. In the familial cases observed by Wolf [*41*], and in this study, there were no immediate adverse effects from thyroid hormones, and the delayed adverse effects were reversible by thyroid hormones. The basic metabolic abnormalities in the familial and the thyrotoxic forms of the syndrome therefore are different, or alternately, there must be an additional reason for thyroid hormones to affect the familial cases differently. If one regards the syndrome of periodic paralysis as of multiple etiology, operative through diverse pathogenetic and pathophysiologic pathways, this finding does not appear surprising.

SUMMARY

The effects of l-triiodothyronine and thyrotropin were investigated in a case of familial periodic paralysis. Hypermetabolism, first induced by the administration of l-triiodothyronine then by thyrotropin, had no immediate adverse effects on the periodic paralysis.

Exacerbations of the disease occurred twice, each time with return of the basal metabolic rate to normal. The increased weakness following withdrawal of l-triiodothyronine was promptly reversed by the administration of thyrotropin. The increased weakness following thyrotropin withdrawal disappeared gradually over twenty-

five days. Thyroid hormones rather than pituitary thyrotropin secretion determined the effects on the periodic paralysis.

Exacerbations of the disease were not associated with depression of the serum potassium levels. Decreased urinary excretion of potassium was noted during the first exacerbation, and decreased excretion of potassium and sodium were noted preceding the second one.

No support could be found for the assumption that the two exacerbations were caused by temporary hyperaldosteronism. The present study points to a difference in the basic abnormality between the thyrotoxic and the familial forms of periodic paralysis.

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Cytomegalic Inclusion Disease and Ulcerative Colitis*

Report of a Case in a Young Adult

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CYTOMEGALIC inclusion disease in human adults is rare. The disorder is associated particularly with serious diseases of the reticuloendothelial system [*1–8*] but this is not true of all cases [*8–13*]. In adults, typical large cells with intranuclear inclusions have been found in the lungs [*1,3–6,8,9,11–13*], adrenal glands [*2,5–8, 12,13*], liver [*1–3,5,6,8,9,13*], spleen [*1,5,8,13*], kidneys [*3,13*], lymph nodes and bone marrow [*8*], and the gastrointestinal tract. The finding of inclusions in the gastrointestinal tract usually has been incidental: in esophageal and gastric ulcers [*10*], duodenal ulcers [*2,5*], amebic colonic ulcers [*9*], and in a small anal tumor [*10*].

In infancy and childhood, however, cytomegalic inclusion disease is more common [*14–17*]. On morphologic grounds, in children and in animals, the cause of the disease was suspected to be a salivary gland virus infection [*9,14–16*]. Subsequent culture of an agent resembling human salivary gland virus from infants and children with cytomegalic inclusion disease has confirmed this impression [*18–22*].

Evidence from three sources suggests that the presence of salivary gland virus is more common than is currently appreciated: (1) the high incidence of the typical inclusion bearing cells at autopsy of unselected infants [*23*]; (2) successful culture of human salivary gland virus from the tonsils and adenoids of apparently healthy children [*24*]; and (3) the prevalence of neutralizing and complement-fixing antibodies to salivary gland virus in children and in adults [*24*]. The possibility that infection occurs when mechanisms of immunity are altered, similar to the situation in certain mycotic infections [*25*], has been stressed recently [*6–8,26*]. This situation may have occurred in the patient reported on herein, who was debilitated and also had received large amounts of adrenal cortical steroids. To our knowledge, the clinical problem to be described has not been reported previously.

CASE REPORT

J. B., an eighteen year old white boy, was admitted to Albert Merritt Billings Hospital because of progressively severe, bloody diarrhea for the previous two months. (Four weeks before admission, a barium enema elsewhere had revealed no abnormalities.) Cramps in the lower part of the abdomen had been noted for three weeks. Hospitalization elsewhere had been necessary two weeks before admission. Administration of prednisone, 40 mg. daily, during the previous hospitalization had had no apparent effect upon the occurrence of ten to fifteen bloody, watery bowel movements daily. At the age of six years, he had vomited for two weeks; bed rest was required for six weeks. No other gastrointestinal difficulty or systemic illness had occurred aside from the usual childhood illnesses. Allergy to a sulfonamide preparation had been discovered during childhood.

On admission the arterial blood pressure was 130/70 mm. Hg; pulse 104 per minute; respirations 24 per minute; and the rectal temperature was 38.6°C. The patient was a pale, emaciated boy, who complained of abdominal distress. The skin was normal, apart from cutaneous changes of weight loss, dehydration and pallor. The ears, eyes, nose, mouth, pharynx and neck appeared normal. No lymphadenopathy was noted. No abnormality, aside from tachycardia, was found in the chest and cardiac examinations. The abdomen appeared normal. No hepatosplenomegaly or other abdominal mass was palpable. Diffuse tenderness in the right and lower left quadrant with slight rebound tenderness was elicited. Bowel sounds were normal. Rectal examination re-

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vealed diffuse tenderness. The genitalia and extremities were normal.

The blood hemoglobin was 12 gm. per cent; red blood cell count 3,400,000 per cu. mm.; white cell count 14,700 per cu. mm.; hematocrit 35 per cent; and erythrocyte sedimentation rate (corrected) 32 mm. per hour; urinalysis, normal; the plasma albumin-globulin ratio was 2.9/2.4 gm. per cent; serum alkaline phosphatase 2.4 units (normal: 1.5–4 units); blood urea nitrogen 13 mg. per cent; serum cholesterol 80 mg. per cent (esters: 60 mg. per cent); serum bilirubin 0.2 mg. per cent total; and normal results of cephalin flocculation, thymol flocculation and thymol turbidity tests. Serial serum protein electrophoretic patterns are recorded in Table 1.

TABLE 1
SERIAL PROTEIN STUDIES

Hospital Day	Total Plasma Protein (gm. %)	Serum Electrophoresis (%)				
		Albumin	Alpha 1 Globulin	Alpha 2 Globulin	Beta Globulin	Gamma Globulin
2	5.3	45.2	9.2	16.3	14.4	13.9
22	3.8	41.6	10.0	14.0	18.6	15.9
29	4.6	44.4	8.2	17.7	14.9	14.8
51	4.2	35.7	9.1	23.9	14.2	17.1
Operation (65th Hospital Day)						
78	5.5	51.2	5.8	11.2	10.3	21.5
118	7.3	42.4	4.4	18.1	14.0	21.2

Initial proctoscopy revealed a diffusely "beefy-red, friable" rectal mucosa. Examination of a rectal swab specimen for ova, parasites and pathogenic bacteria was negative. Ten subsequent stool examinations for ova, parasites and pathogenic bacteria also were negative. The poor clinical status of the patient precluded roentgenographic examination of the colon. Roentgenograms of the chest revealed no abnormalities.

Treatment included the intravenous administration of dextrose and electrolytes, penicillin, streptomycin and hydrocortisone, 150 mg. daily. The patient was allowed nothing orally. Vitamins, moderate sedatives and analgesics also were given.

The bloody diarrhea persisted. The patient's temperature rose daily to 40°c. Intravenous ACTH, 30 units daily, was instituted on the seventh hospital day. The administration of intravenous hydrocortisone was decreased slowly. Gradual improvement ensued, with reduction of fever, diminution of the bloody diarrhea, and cessation of abdominal pain and tenderness. Oral intake was begun on the twenty-first hospital day. Intramuscular ACTH was substituted for intravenous ACTH and the dosage then gradually diminished, as hydrocortisone, 200 mg. daily, was prescribed orally. The status of the patient improved until the forty-eighth hospital day. Bowel movements had become tan and formed, and numbered three to four daily. At that time fever and bloody diarrhea recurred. Eight blood cultures and two urine cultures were negative. The patient's status declined despite reinstitution of hydrocortisone intravenously, initially, 150 mg. daily, later 250 mg. daily, intravenous penicillin, chloramphenicol, and later novobiocin, and whole blood and plasma. The progressive clinical deterioration and massive blood loss per rectum (bleeding and clotting studies were normal) despite maximal medical treatment necessitated surgery on the sixty-fifth hospital day.

At operation several hundred milliliters of clear orange ascitic fluid were encountered, partially in jelly-like clots. There was no free pus. The entire colon was thickened and edematous, with a clear mucoid serosal exudate. The haustra were preserved. The area of greatest involvement extended from the cecum to the splenic flexure; the sigmoid and rectosigmoid appeared least involved. There was no perforation and no evidence of abscess formation. The remainder of the abdominal organs appeared essentially normal. A subtotal colectomy was performed, and an ileostomy was established in the right lower quadrant of the abdomen. The rectal stump was closed below the peritoneal reflection.

Despite a stormy postoperative course, gradual recovery ensued. Peri-ileostomy drainage and abscess formation developed, followed by slow healing. The administration of adrenal cortical steroid medication was decreased slowly, concomitantly with the patient's improvement; it was discontinued on the 125th hospital day. Proctoscopy on the 129th hospital day revealed a mucopurulent exudate over the rectal mucosa. Culture revealed numerous bacterial pathogens, but culture of a biopsy specimen obtained at proctoscopy as well as cultures of urine and a specimen of colon frozen at operation, for salivary gland virus (human fibroblast tissue culture) were negative. Following increased oral intake and gradual ambulation with physical therapy, the patient was discharged on the 143rd hospital day. At that time the hemoglobin was 12.1 gm. per cent; plasma albumin 3.4 gm. per cent; and serum cholesterol 270 mg. per cent.

Pathological findings: The specimen included the colon, from cecum to rectum, in continuity with a 3 cm. segment of terminal ileum, and the vermiform appendix; portions of omentum and mesentery were attached. (Fig. 1.) The colonic mucosa was coarsely pebbled, with edematous soft bulging lobules comprising most of the surface. On the tips of some of these bullous lobules were adherent yellow-green membranes. Situated between the lobules were scattered round or oval ulcers, more than a dozen in all, ranging from 0.2 cm. in diameter to 5.5 by 3.5 cm. across. The long axis of the larger ulcers was parallel to the



FIG. 1. Gross appearance of the surgical specimen.

long axis of the colon. Ulceration was more severe in the transverse colon, where the largest ulcer was located, and in the descending colon. There was lesser involvement in the cecum and right colon. The larger ulcers were covered by adherent, tough, yellowish-brown membranes. Although well defined, the margins were irregular or scalloped, with the edematous

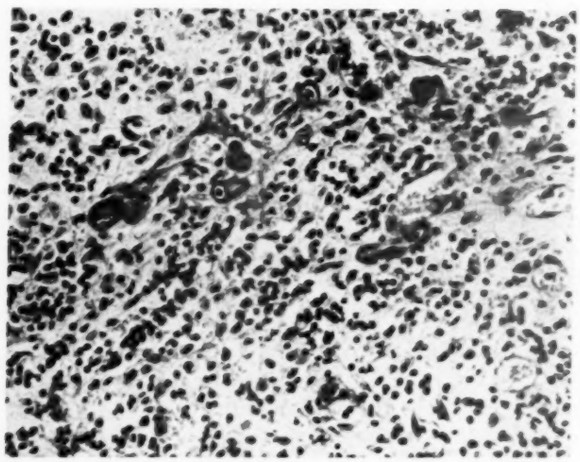


FIG. 2. Typical cytomegalic inclusions, in floor of an ulcer. Original magnification × 270.

lobules forming the borders. Situated throughout the colon, but more numerous in the transverse and descending parts, were approximately a dozen short cylindrical, soft, smooth, polypoid mucosal projections measuring from 0.8 to 1 cm. in length; these structures resembled the stalks of truncated polyps. Several mucosal "bridges" also were present. The non-ulcerated mucosal surfaces ranged from fiery red to pale pink. The wall of the colon was thickened, largely due to the increased breadth of the edematous mucosa and submucosa; although there was partial loss of pliability and elasticity, the muscularis proper was only slightly thickened. The circumference of the colon ranged from 5 cm. in the transverse part to 8 cm. in the ascending portion. The serosa was injected and edematous, but was glistening and smooth, with the usual luster; a few scattered small red fibrous tags were present. The appendix and terminal ileum presented no unusual features. The mesenteric nodes were

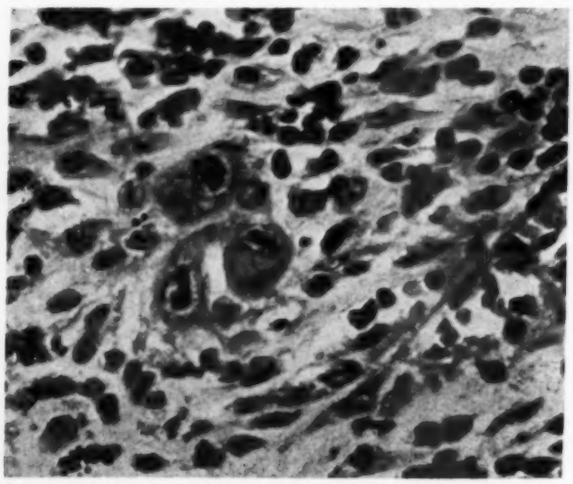


FIG. 3. Cytomegalic inclusions. Original magnification × 950.



FIG. 4. Angiitis, interstitial inflammation and edema, in bullous lobule. Original magnification × 140.

not enlarged or prominent. The mesenteric and omental fat was soft and pale yellow, with no evident abnormalities.

The microscopic appearance was distinctly different from that of non-specific ulcerative colitis. The major distinguishing feature was the presence of dozens of cellular inclusions, typical of cytomegalic inclusion disease. (Figs. 2 and 3.) The affected cells were enlarged to 20μ or more, with swollen nuclei containing a larger, round or kidney-shaped inclusion, surrounded by a clear zone. Punctate orbital bodies were evident at the nuclear membrane, and minute granular cytoplasmic inclusions were visible in some cells. The distribution of the inclusions corresponded rather closely to the two zones where the inflammation was most intense; these were (1) the floors of the ulcers, and (2) the tips of the edematous lobules with adherent membranes (actually pseudomembranes). In the floors of the ulcers there was random arrangement of the inclusion-laden cells within the mixture of inflammatory cells and fibroblasts. (Fig. 2.) In the bullous lobules, however, there was distinct localization of inclusions within the nuclei of vascular endothelial cells, often with associated angiitis, or even frank necrosis. (Fig. 4.) Examples of typical inclusions in other locations were few. Several were found in smooth muscle cells of the intestinal wall, and in cells of the myenteric plexus. One endothelial inclusion was encountered in a small vessel immediately adjacent to a mesenteric lymph node (Fig. 5); some of the endothelial cells in serosal vessels were similarly involved. No inclusions were found in epithelial cells of the colonic mucosa or within lymph nodes.

As to the general pattern of the inflammation, acute ulceration predominated, though subacute and healed ulcers could be found. (Fig. 6.) The smallest (and presumably the earliest) lesions were tiny patches of cryptitis, involving two or three glands; the lumens were dilated and contained a mixture of leukocytes and mucus. The next larger lesions, far more numerous and conspicuous, were the discrete foci at the tips of the bullous lobules. (Fig. 7.) These were characterized by necrosis of epithelium and lamina propria, with vascular dilatation and engorgement, angiitis, leukocytic infiltration, and exudation of fibrin at the surface, the last forming a pseudomembrane. The underlying submucosa was massively edematous, producing the bullous appearance; fibrinous exudate, cellular infiltration and vascular dilatation were present here, as well. The cytomegalic inclusions were a constant feature in endothelial nuclei of dilated engorged vessels. The ulcers appeared to form by peripheral extension and coalescence of the inflammation and necrosis. Some of the ulcers were covered by fibrinopurulent exudate. The bases were

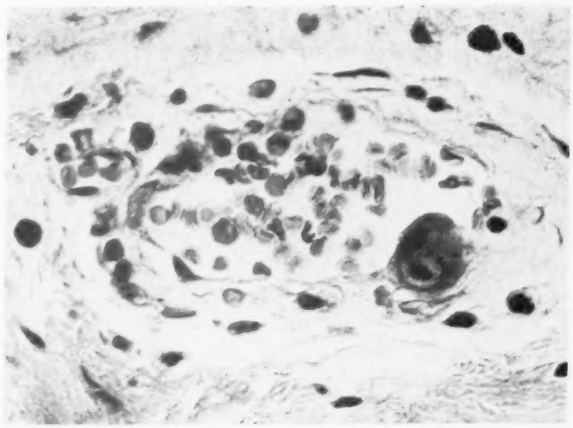


FIG. 5. Cytomegalic inclusion in endothelium of mesenteric vessel. Original magnification × 950.

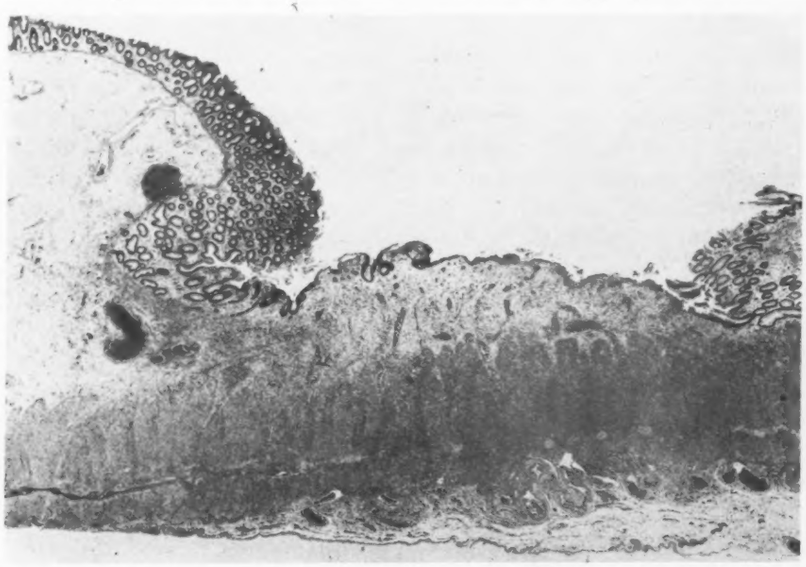


FIG. 6. Healing ulcer, with growth of epithelium at the base. Original magnification × 20.

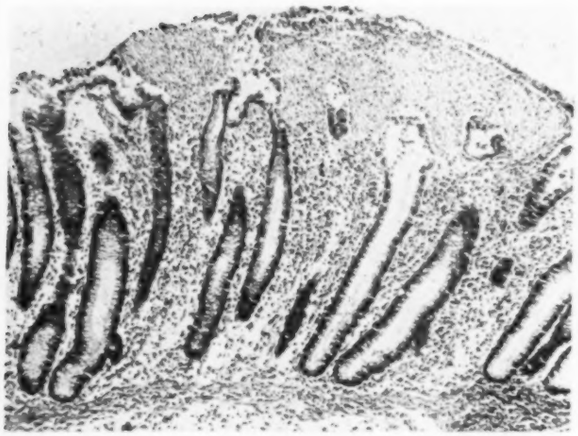


FIG. 7. Superficial inflammation and necrosis of colon mucosa. Original magnification × 80.

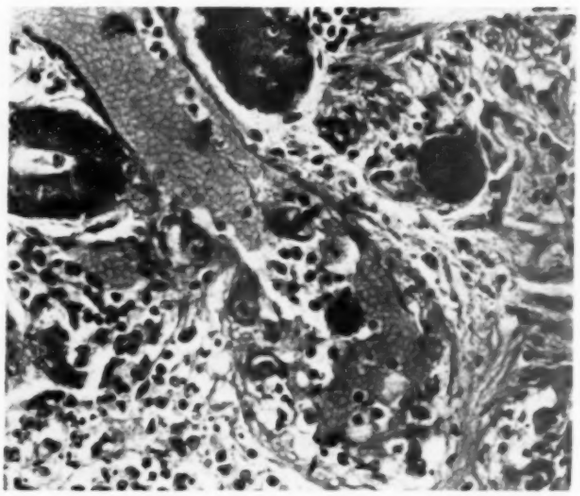


FIG. 8. Cytomegalic inclusions in endothelium at margin of ulcer in colon of patient with lymphoma, disseminated cytomegalic inclusion disease, ulcerative enteritis and intractable diarrhea. Original magnification × 270. (This photograph reproduced by the courtesy of Cedars of Lebanon Hospital.)

composed of granulation tissue densely infiltrated by chronic inflammatory cells, with a sprinkling of neutrophils; cytomegalic inclusions were abundant. The majority of ulcers were located above the muscularis proper, but a few had extended to the serosa.

Lesions like those in the colon were found in the mucosa of the appendix. However, the terminal ileum was not ulcerated or scarred, although an occasional cytomegalic inclusion was observed in the endothelium of vessels of the ileal serosa.

COMMENTS

The case of an eighteen year old boy who thus far has survived cytomegalic inclusion disease, associated with ulcerative colitis, has been presented herein. Attempts to culture the human salivary gland virus (using parts of the frozen surgical specimen, urine, and tissue obtained postoperatively by proctoscopic biopsy) were not successful. Furthermore, no antibodies to human salivary gland virus have been demonstrated to date in the patient's serum. Nevertheless, the appearance of the inclusions is regarded as virtually diagnostic, and their identity in this case has been unanimously affirmed by all consultants.

We are unable to say whether the primary disease in this patient was non-specific ulcerative colitis, complicated by salivary gland virus infection incident to debility and the therapeutic use of adrenal cortical steroids (as has been suggested by others [*3,6–8,26*]), or whether the primary disease was infection with salivary gland virus resulting in a clinical picture simulating non-specific ulcerative colitis. The rarity of the finding of cytomegalic inclusions in tissues from patients with non-specific ulcerative colitis favors the latter possibility, although some instances of salivary gland virus infection, with ulcerative enteritis, may have been unrecognized in the past [*27*].

The possibility that cytomegalic inclusion disease occurs when a latent form of salivary gland virus becomes manifest, owing to alteration in mechanisms of immunity, has been widely recognized; this subject has been reviewed recently [*26*]. In this patient no deficiency of gamma globulin was demonstrated by electrophoresis; however, this does not necessarily signify that the mechanisms of immunity were intact. Debility is frequently but not always a factor [*10*]. Certain chemotherapeutic agents have been indicted as contributing factors in salivary gland virus infection, but the disease was known before these agents were in use and it has been observed in patients not receiving such drugs. Vitamin deficiency [*11*] was not known to exist in our patient. The increased susceptibility of proliferating endothelium to salivary gland virus was observed recently in a natural infection in a child, and in experimental infection in mice [*28*]. Certainly granulation tissue, with proliferating endothelium, abounds in ulcerative colitis, and such proliferating tissue has been noted in adults with cytomegalic inclusion disease and ulceration of the intestinal tract, and in an anal tumor [*2,5,10*]. However, on the basis of our study of this patient, and another patient observed by one of us, (Fig. 8), it appears that

vascular endothelial cells of the colon in general are susceptible to the virus, e.g., that the susceptibility is not limited to proliferating endothelial cells. Furthermore, this susceptibility of vascular endothelium appears to play a role in the pathogenesis of the ulceration, for there was a constant association of endothelial inclusions, angiitis and ulceration. This complex may be nothing more than a reflection of the stereotyped pattern of reaction of the colon to injury [*29*], for the endothelial inclusions in other locations did not appear to be inimical.

It has been suggested that salivary gland virus infection may mimic or cause certain of the proliferative reticuloendothelial diseases in which salivary gland virus was once regarded as a secondary invader [*13,26*]. Similarly, the finding of cytoplasmic inclusions in the colons of patients with ulcerative colitis has suggested a possible viral etiology for non-specific ulcerative colitis [*30*]. Although this does not appear to be the most likely possibility at present, more data are needed to settle the issue.

SUMMARY

Cytomegalic inclusion disease in the colon of a young man with a clinical picture simulating non-specific ulcerative colitis is described. The patient has survived to date.

Etiologic and contributing factors are discussed. The occurrence of the disease appears to be related to a combination of circumstances, perhaps including latent viral infection, reduced immunity incident to debility, disease of the reticuloendothelial system, and administration of certain drugs.

The affinity of the salivary gland virus for the vascular endothelium of the colon and the role of endothelial involvement in the pathogenesis of the ulceration are emphasized.

ADDENUM

During the year following surgery, results of repeat studies for antibody to salivary gland virus, carried out by Dr. Wallace P. Rowe, have been positive.

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Report of a Case*

Mrs. L. S., 44, was admitted to the hospital on April 17, 1959, with massive ascites, 3-plus edema of the legs and moderate pulmonary congestion. Three previous admissions had established that she had rheumatic heart disease with cardiac enlargement, atrial fibrillation and mixed valvular lesions.

She was placed on a regimen of bed rest, digitalis and 0.5 Gm. of sodium daily. On treatment which included mercurials parenterally, hydrochlorothiazide, KCl, NH_4Cl, aminophylline, prednisone, acetazoleamide and lysine monochloride the patient lost 15 pounds, but her ascites did not diminish noticeably and her weight remained within the range of 130 to 135 pounds from May 1 to May 30.

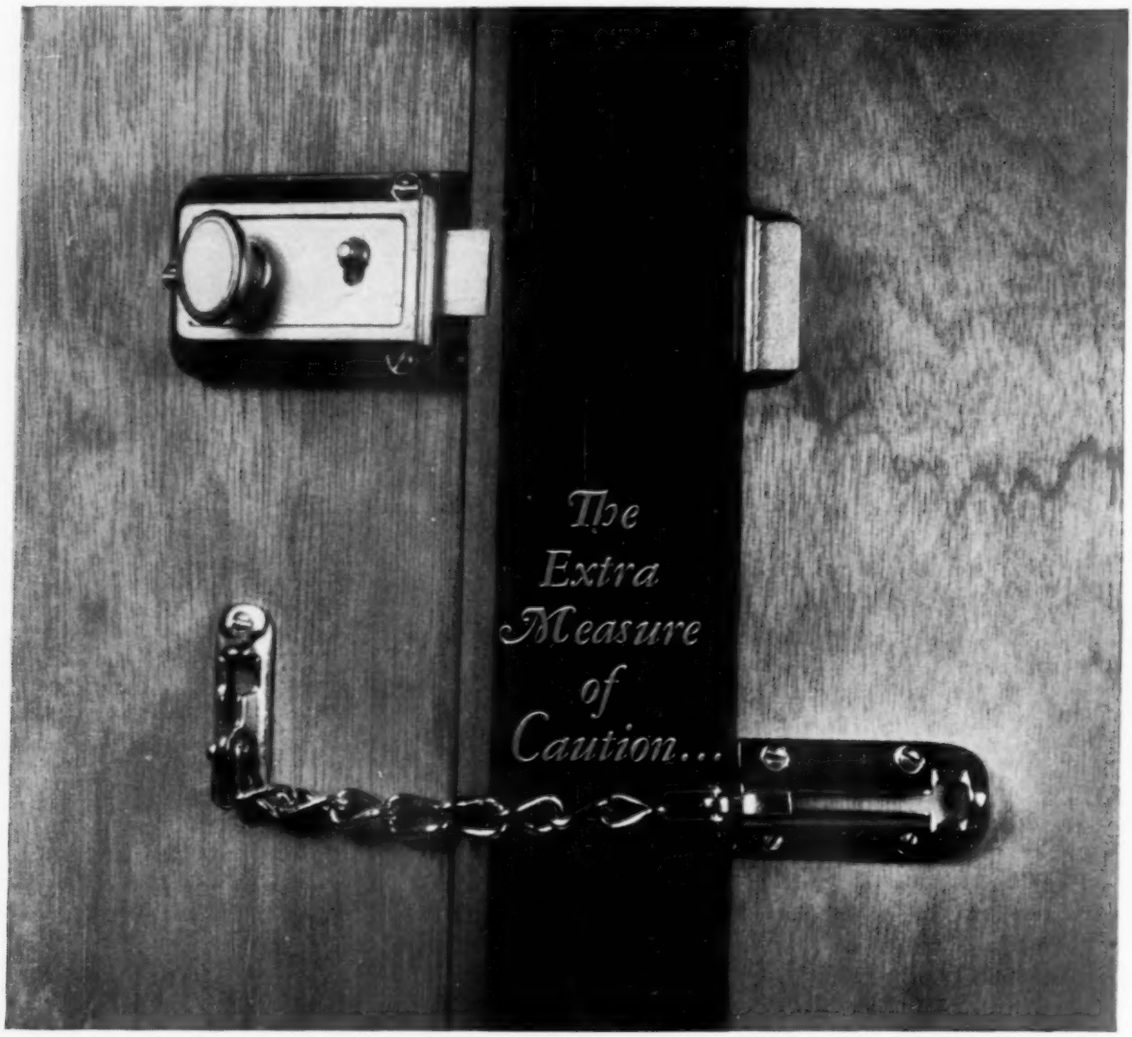
On May 30, 100 mg. of Aldactone q.i.d. was added to her regimen. Progressive and continuous diuresis followed. Weight dropped from 130 to 107 pounds, her normal weight. The patient was discharged on June 14 completely free from ascites and peripheral edema.

She was maintained on digitalis and hydrochlorothiazide and had no further weight gain until December 1959. She was then given 400 mg. of Aldactone daily for five days and again achieved dry weight, which was maintained as of February 1960.

SUPPLIED: Aldactone (brand of spironolactone) is supplied as compression-coated yellow tablets of 100 mg.

*Klass, A.: Cur. Therap. Res. 2:322 (July) 1960.

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1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958.
2. Moser, K. M.: Disease-a-Month, Chicago, Yr. Bk. Pub., Mar., 1960, p. 13.

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Case history courtesy of Joel Goldman, M.D., Johnstown, Pa.
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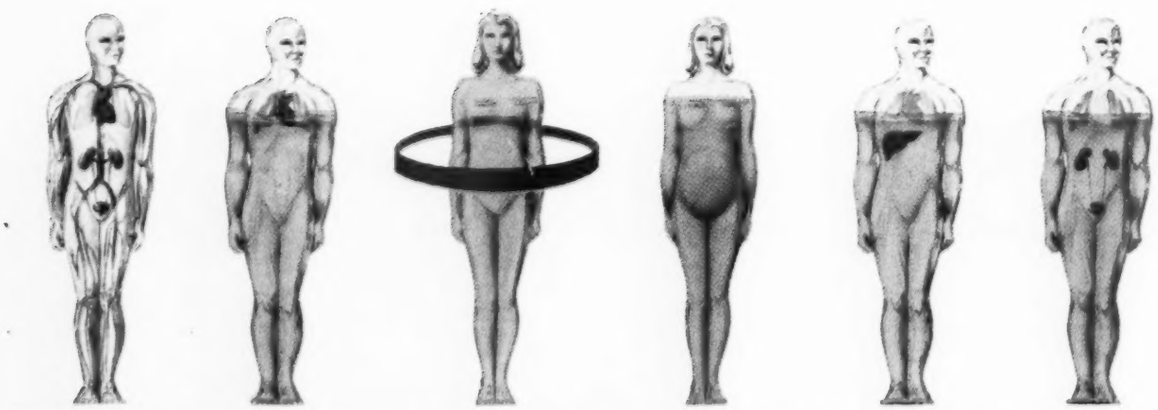
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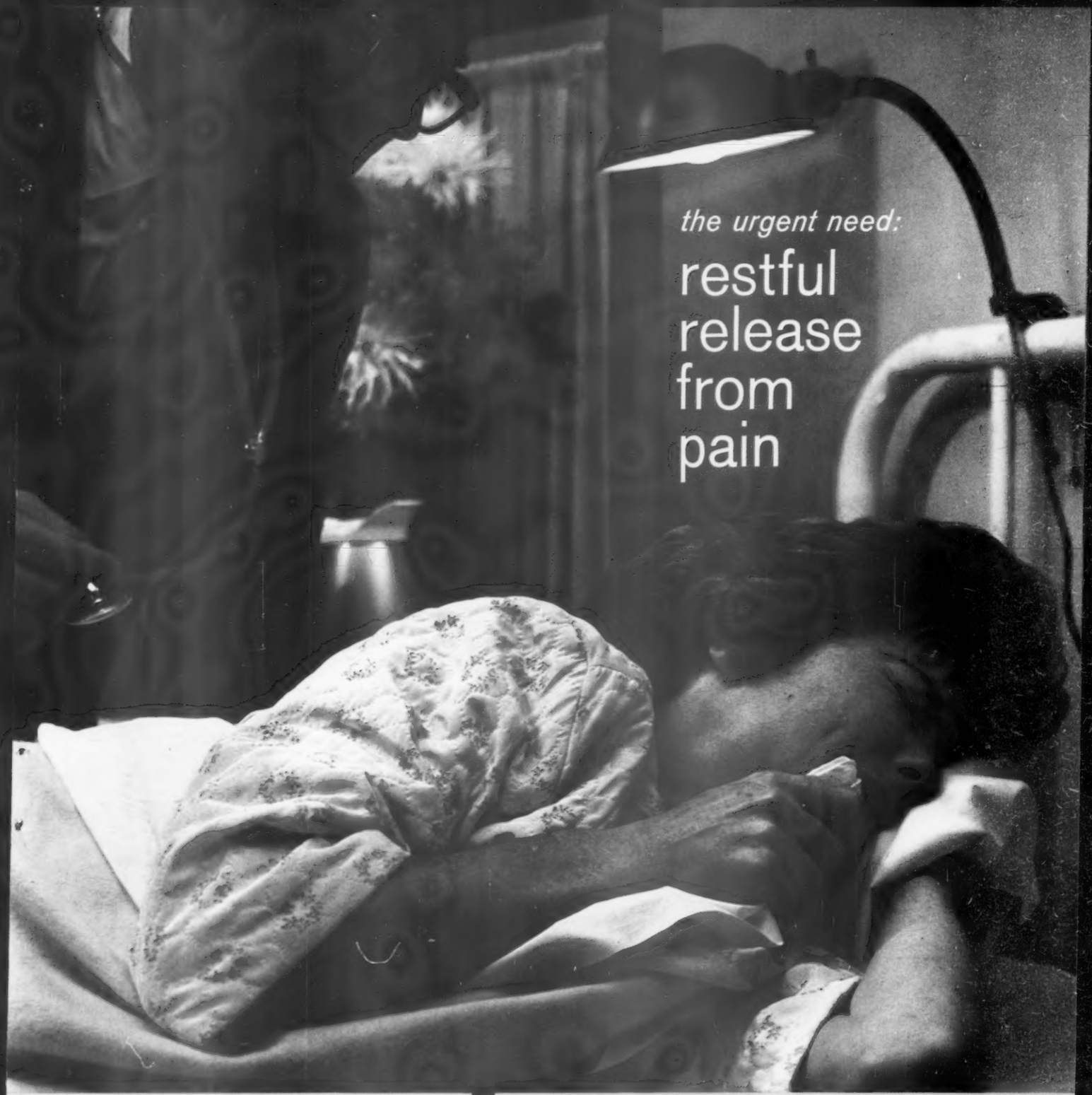
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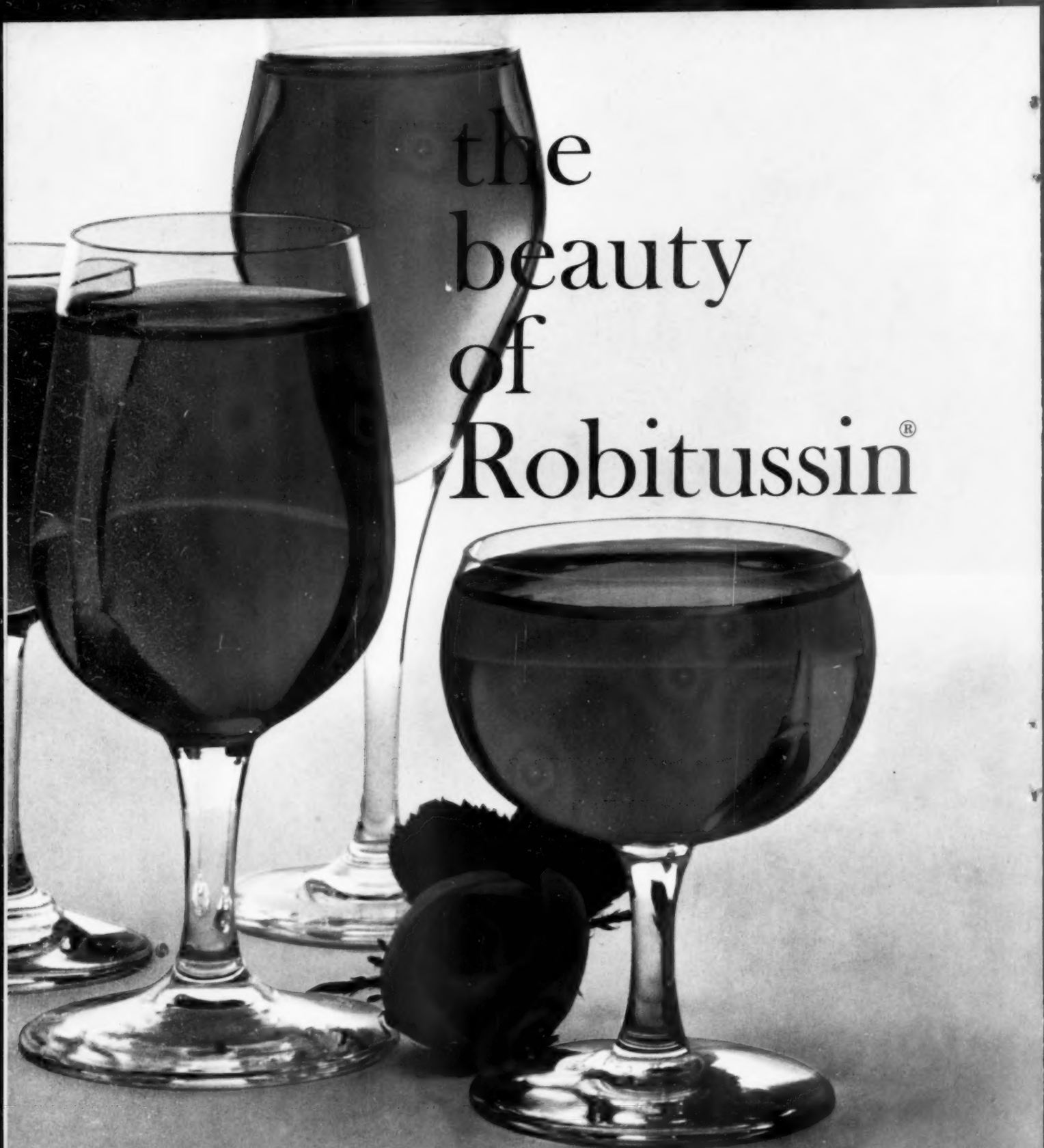
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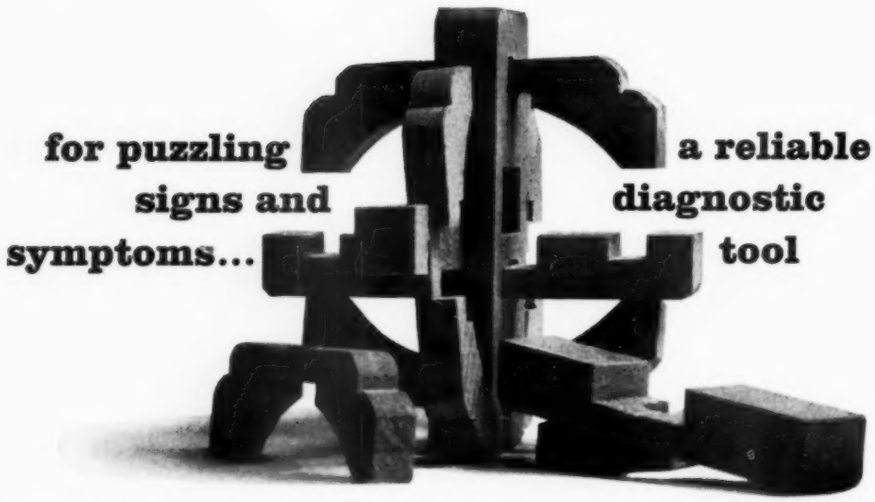
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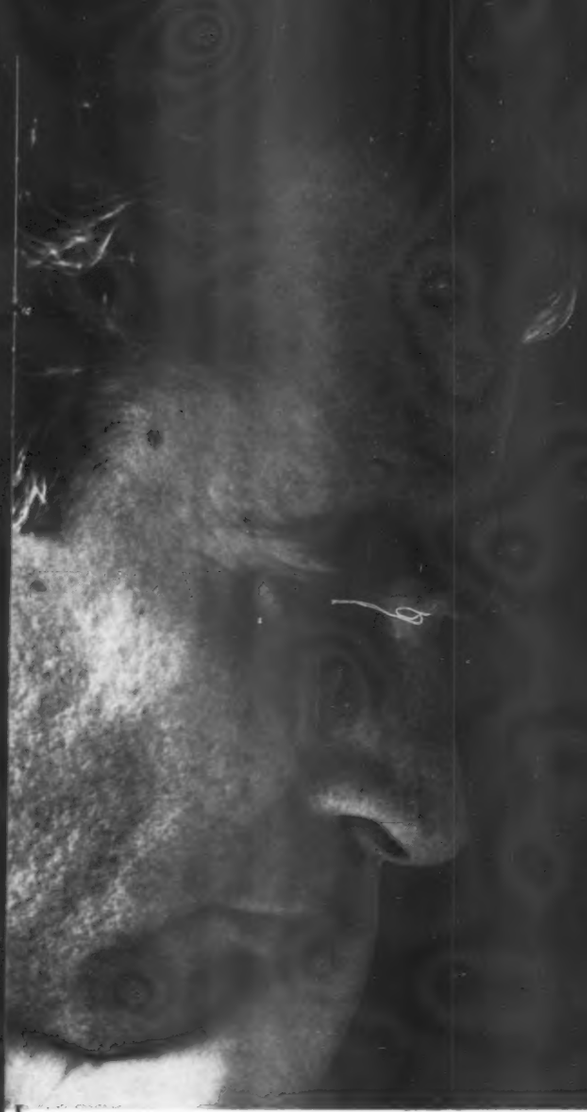
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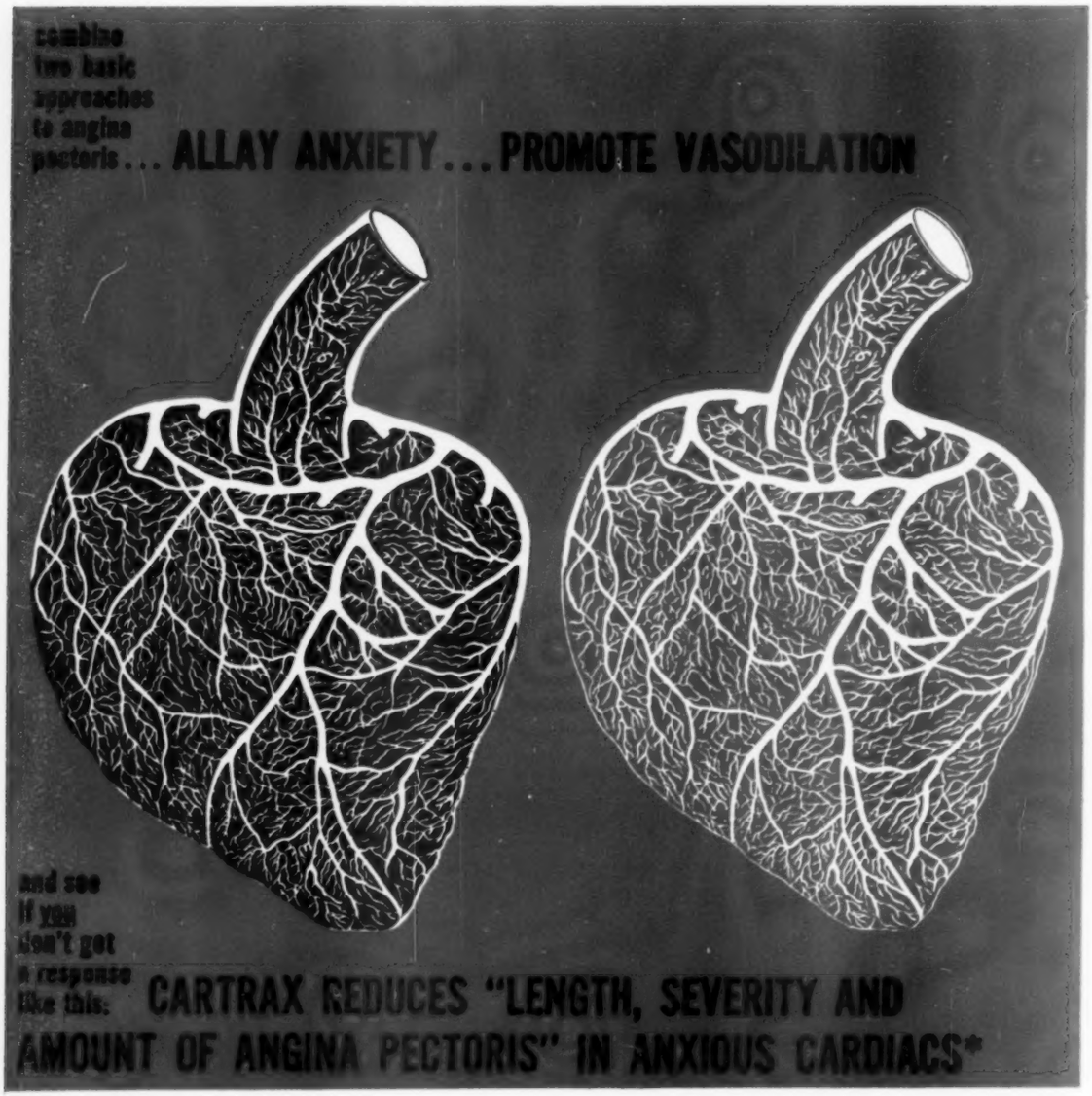
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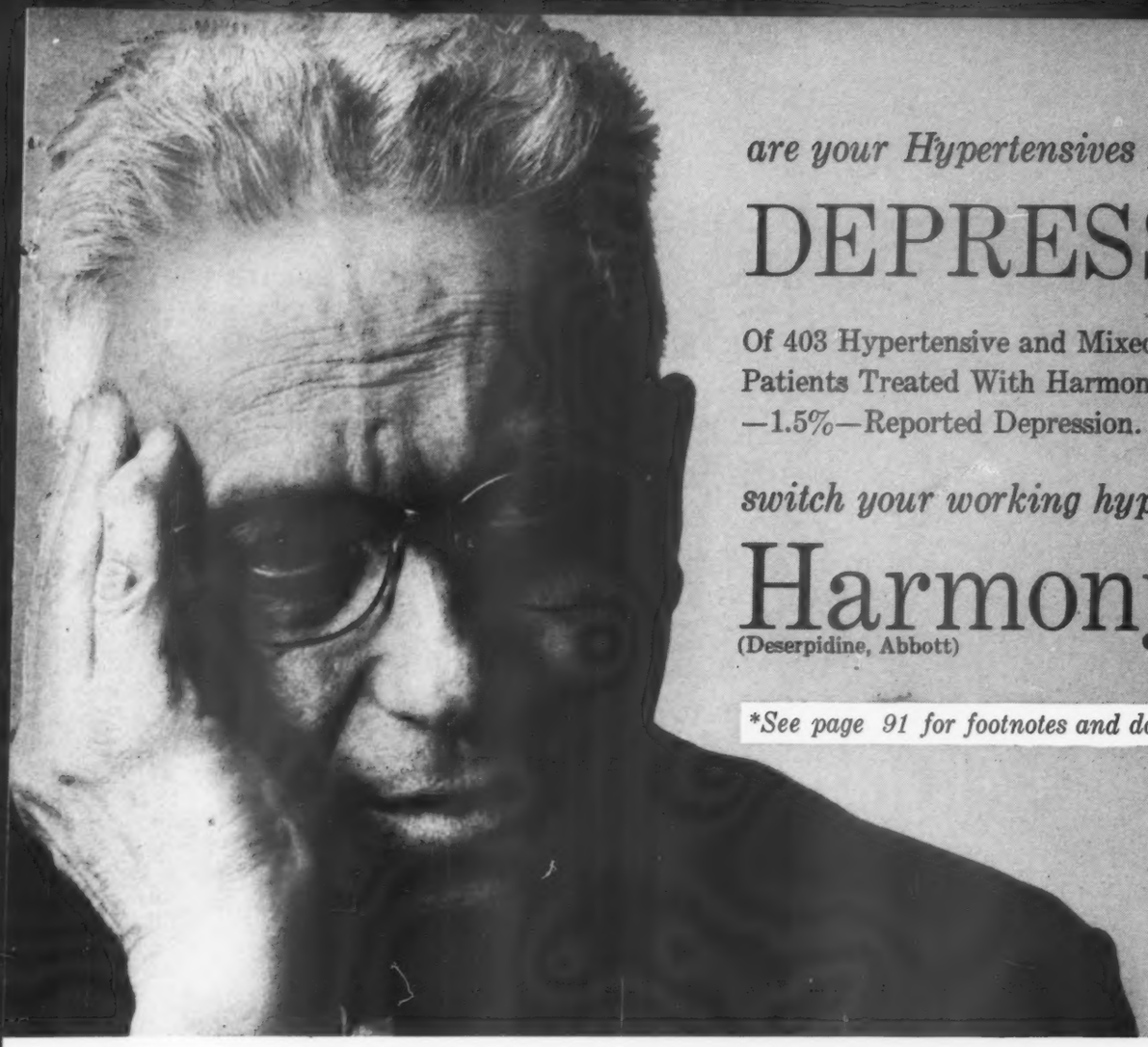
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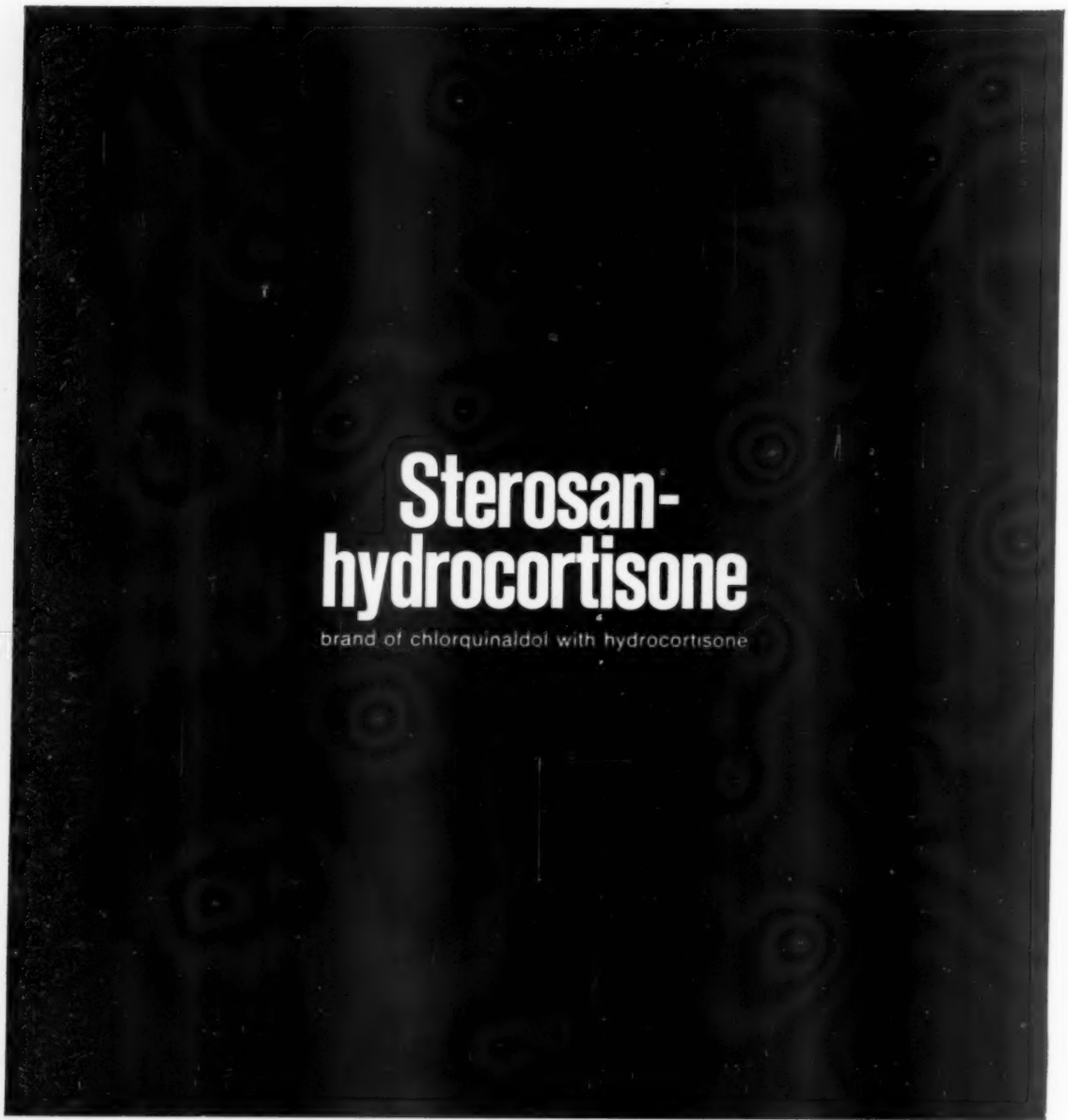
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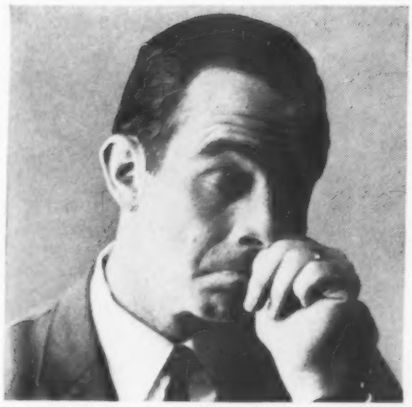
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1. Billow, B.W. et al., The Use of a New Rauwolfia Derivative, Deserpidine, in Mild Functional Disturbances and Office Psychiatry, N.Y. J. Med., 59:1789, May, 1959.
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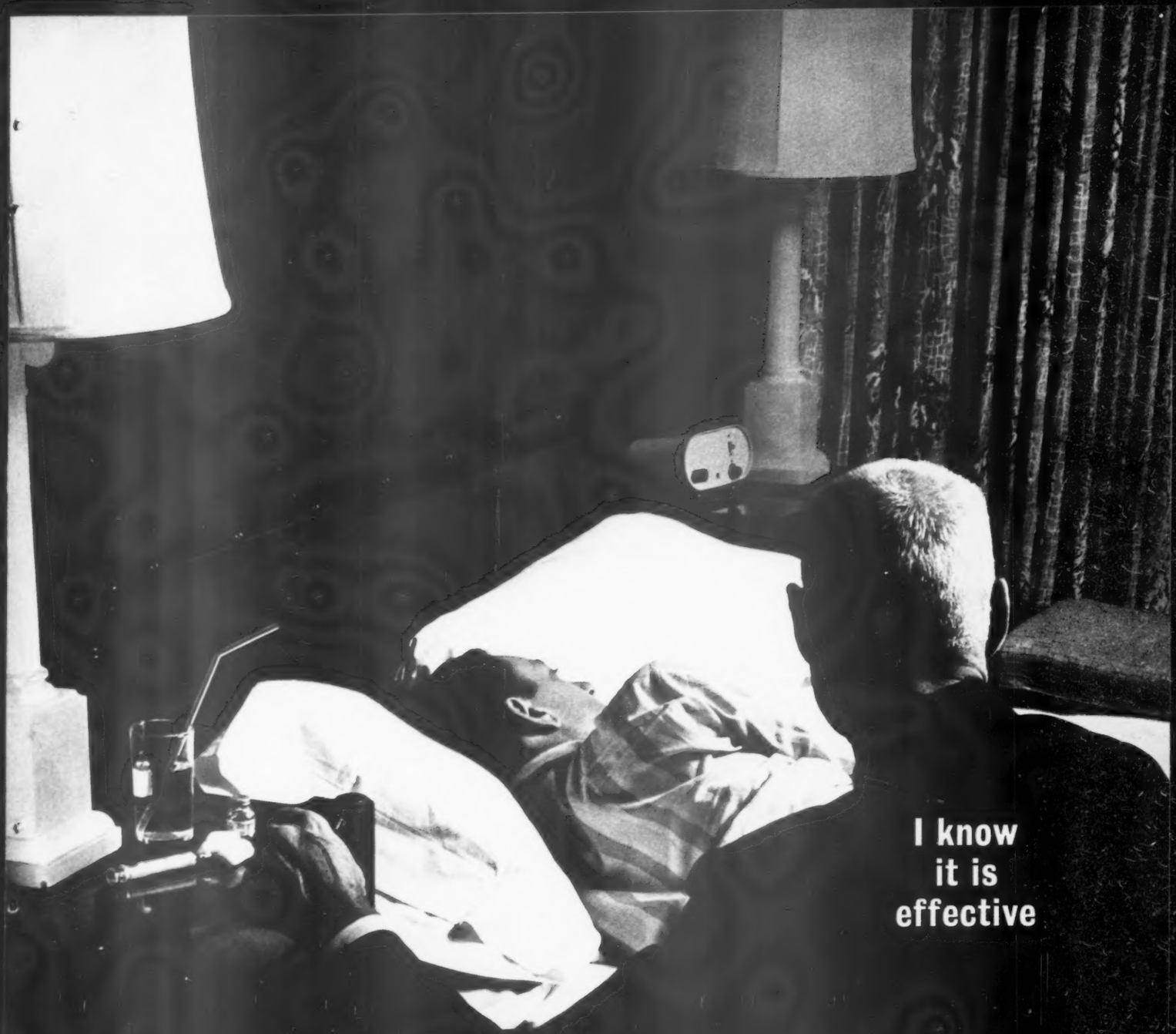
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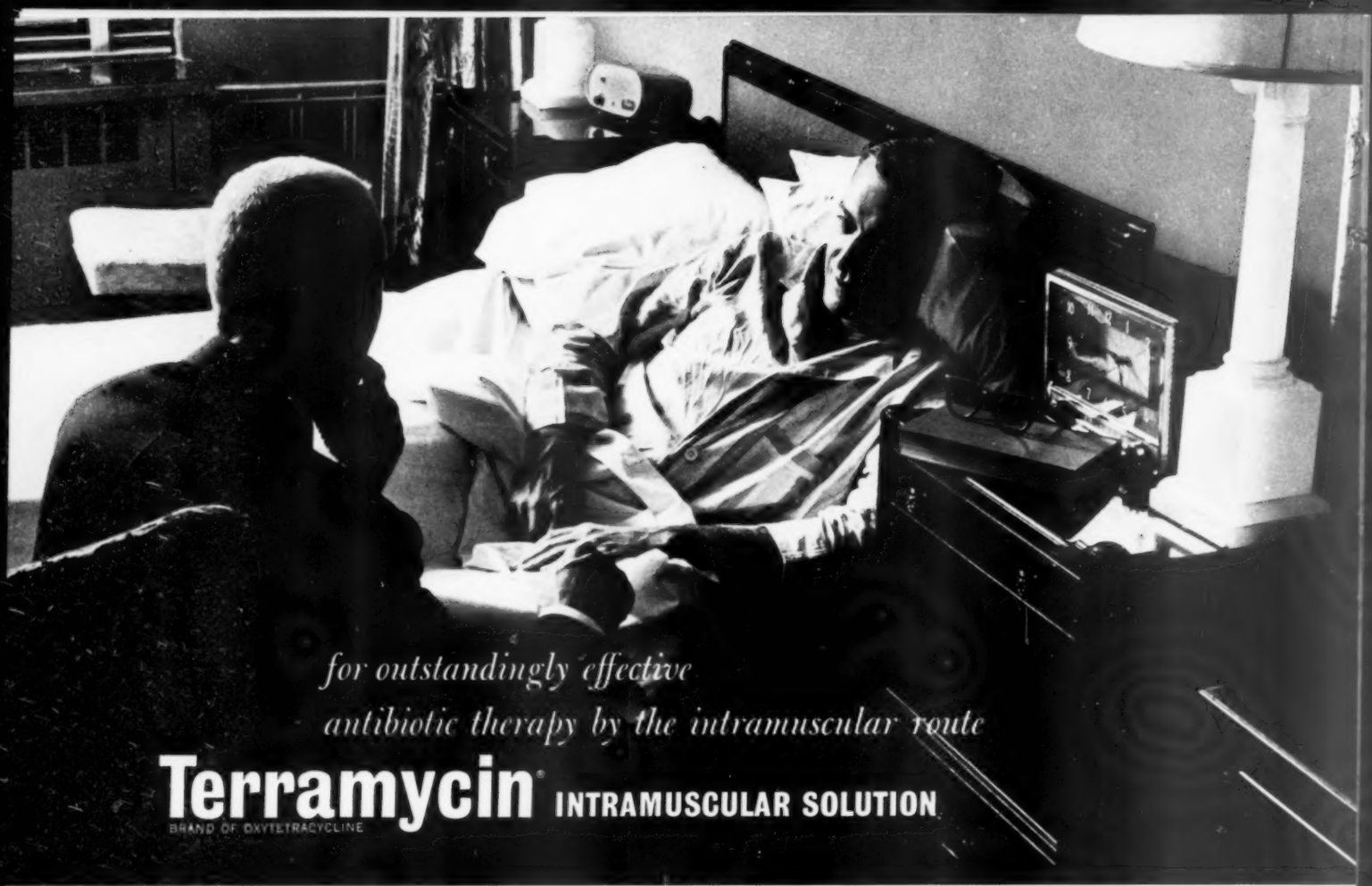


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ADMINISTRATION AND DOSAGE: For intramuscular injection only. Adults: Unless otherwise specified, a dose of 100 mg. every 8-12 hours, or a single daily dose of 250 mg. should be adequate for most mild or moderately severe infections. In *severe* infections, 100 mg. every 6-8 hours or 250 mg. every 12 hours may be necessary. Infants and children should receive proportionately less in accordance with age and weight of patient, and severity of infection.

SIDE EFFECTS AND PRECAUTIONS: Aside from occasional mild pain at injection site, adverse reactions (including allergic) have been rare. As with all I.M. preparations, injection should be made within the body of a relatively large muscle. After insertion of needle, aspiration should be attempted before injecting to avoid inadvertent administration into a blood vessel; care should always be taken to avoid injecting into a major nerve or its surrounding sheath. Subcutaneous and fat-layer injection may cause mild pain and induration, which may be relieved by an ice pack.

Use of antibiotics may result in an overgrowth of nonsusceptible organisms — particularly monilia and resistant staphylococci. If a new infection caused by a resistant pathogen appears, discontinue the medication and institute appropriate specific therapy as indicated by susceptibility testing.

SUPPLIED: *Terramycin Intramuscular Solution,* 10 cc. multidose vial, 50 mg./cc., also available as 2 cc. prescored glass ampules, containing 100 mg. or 250 mg., packages of 5 and 100. For rapidly fulminating or critical infections—*Terramycin Intravenous,* in vials of 250 mg. and 500 mg. (buffered with 1 Gm. and 2 Gm. ascorbic acid, respectively). In addition, a variety of other systemic and local dosage forms are available to meet specific therapeutic requirements — including *Cosa-Terramycin Capsules, Cosa-Terrabon Oral Suspension* and *Cosa-Terrabon Pediatric Drops.*

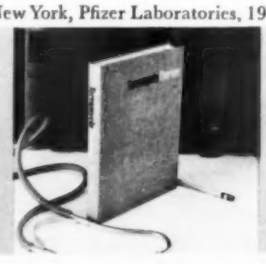
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†*Terramycin Therapy,* p. 7, New York, Pfizer Laboratories, 1960.

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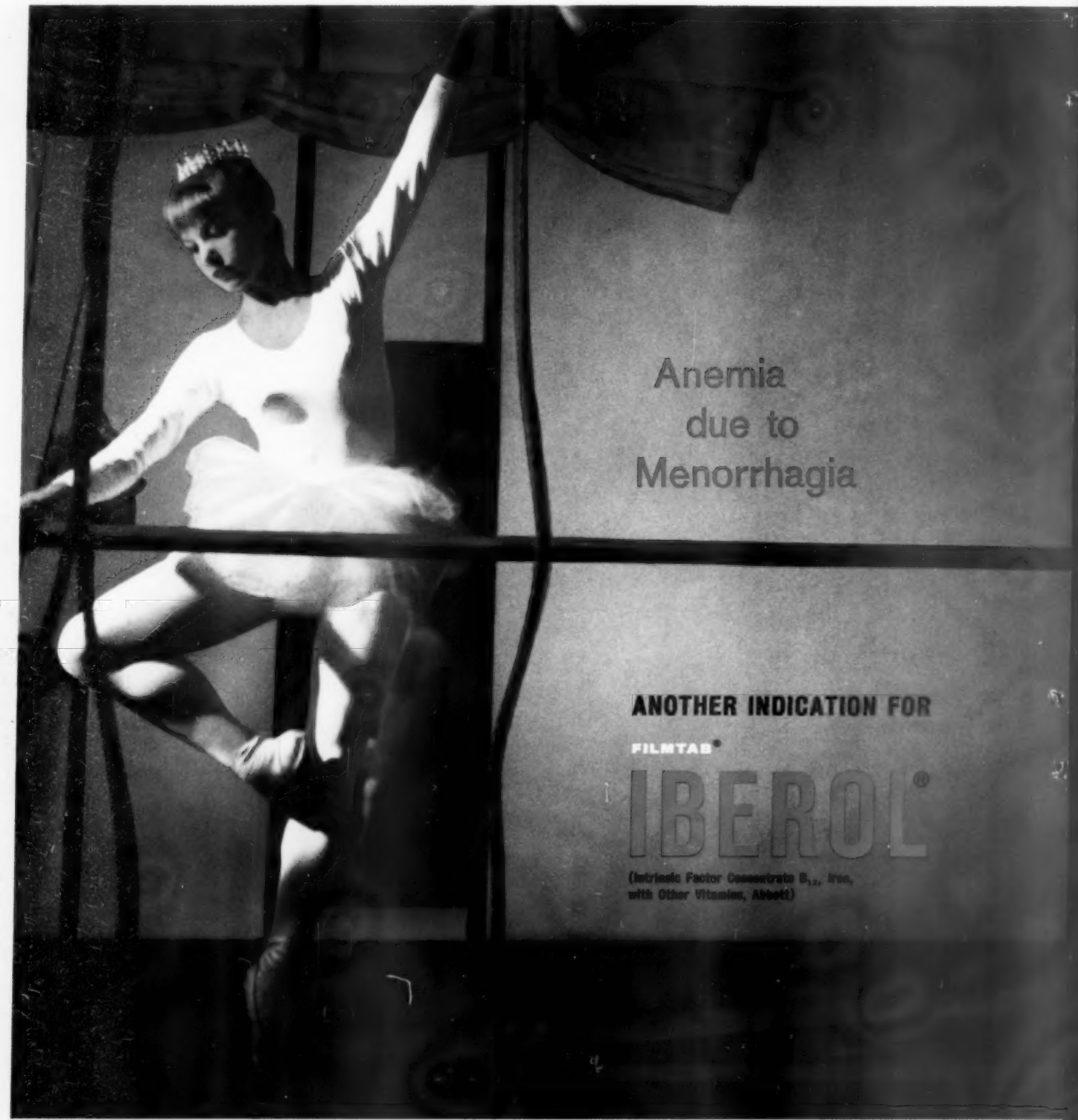
The last one worked pretty good—for a week. Now it starts again... the searching and the scratching... and the scrutinizing of labels. What she needs won't be found next to a head of lettuce. Next time you see the symptoms... do her a favor... give her the word and a prescription for Selsun. Available only at pharmacies.

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PLUS THE ESSENTIAL B-COMPLEX

Vitamin B_{12} with Intrinsic Factor Concentrate	1 N.F. unit (oral)
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Riboflavin	6 mg.
Nicotinamide	30 mg.
Pyridoxine Hydrochloride	3 mg.
Calcium Pantothenate	6 mg.

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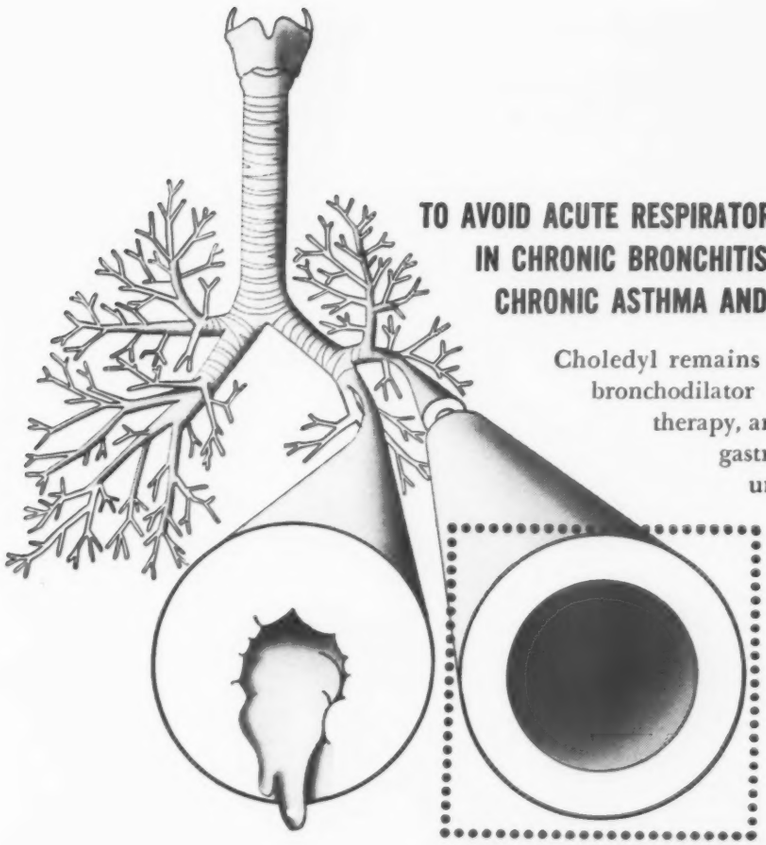
Ascorbic Acid	150 mg.

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*Folic Acid does not control neurological symptoms of pernicious anemia.

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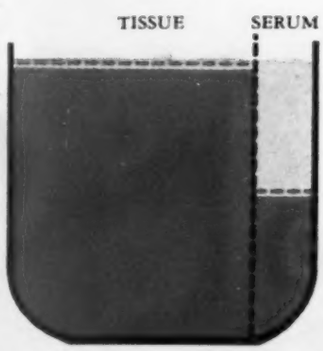
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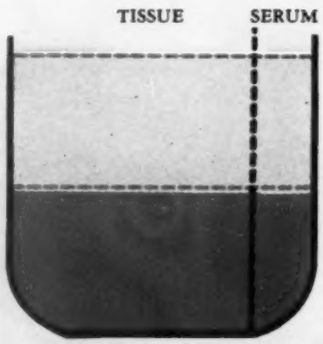
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effect on body pool of cholesterol



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There is no evidence that tissue cholesterol is reduced even in the face of serum cholesterol reduction.



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particularly those with high cholesterol levels, coronary artery disease, and generalized atherosclerosis

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CAUTION: Since long-term MER/29 therapy may be necessary, periodic examinations, including liver-function tests, are desirable. Also, since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug is contraindicated in pregnancy.

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(triparanol)

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REFER TO PDR
PAGE 813

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1. Lehrer, H. W., et al.: Northwest Med. 75:1249, 1955.
2. Smith, Richard T.: New York Med. 8:16, 1952.

for functional disorders of menopause...
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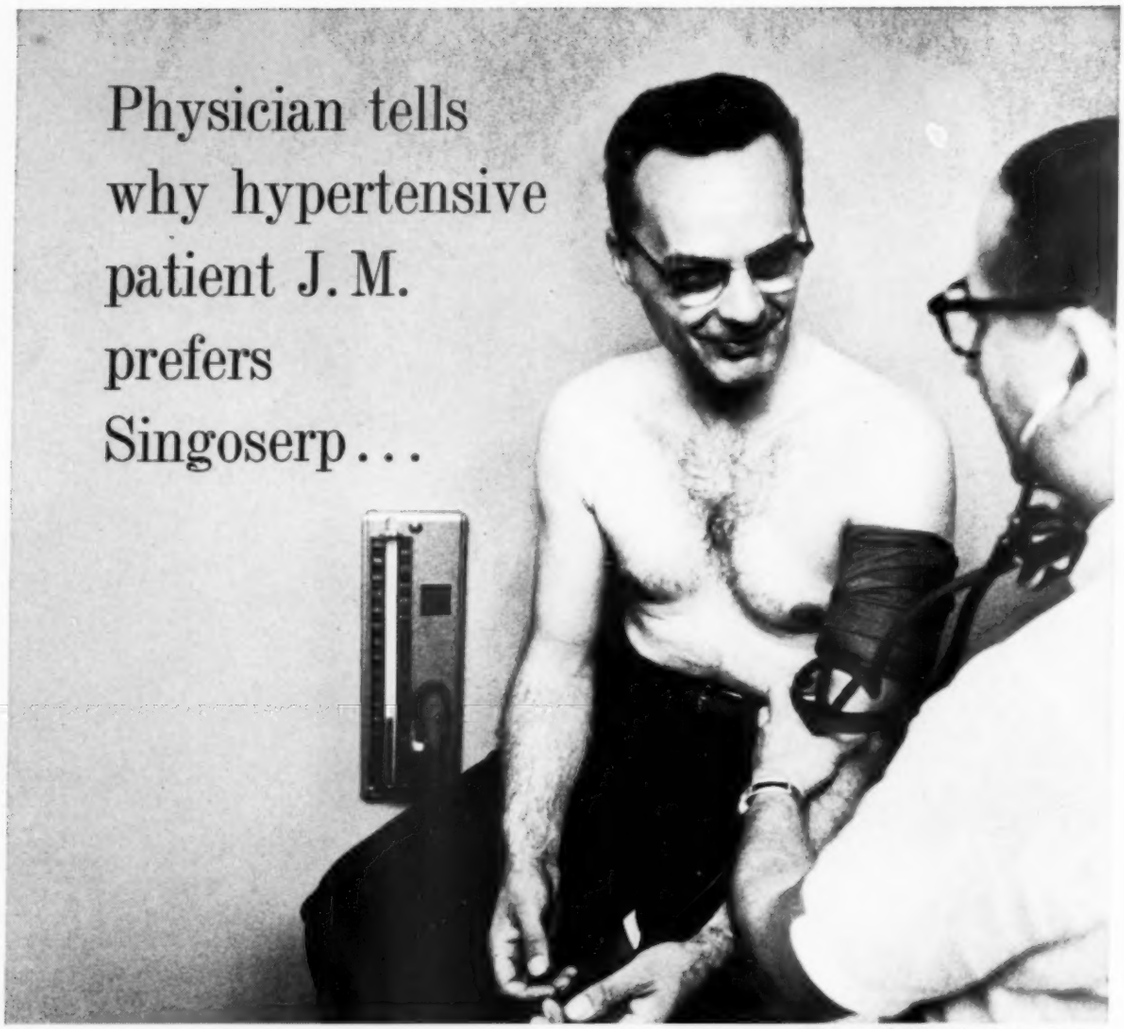


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Physician's report: J. M., a salesman, had a 16-year history of hypertension. Blood pressure at first examination was 190/100 mm. Hg. Whole root rauwolfia lowered pressure to 140/80 — but side effects were intolerable. Singoserp further reduced pressure to 130/80 and eliminated all drug symptoms.

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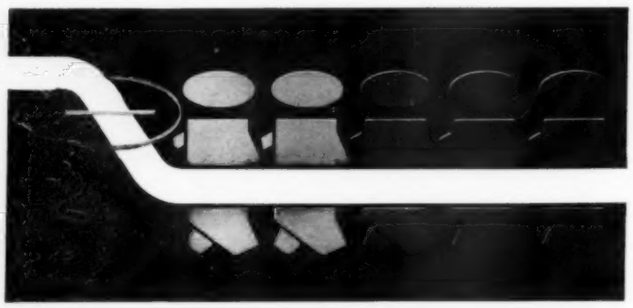
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1. Cornely, D. A., and Ritter, J. A.: N-acetyl-p-aminophenol (Tylenol Elixir) as a Pediatric Antipyretic-Analgesic, J.A.M.A. *160*-1219 (Apr. 7) 1956

2. Mintz, A. A.: Management of the Febrile Child, J. Ky. Acad. Gen. Pract. *5*:26 (Jan.) 1959.

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for example—when control with insulin is unsatisfactory because of intolerance, atrophy at site of injection, or overinsulinization, consider replacement or reduction of insulin dosage with DIABINESE. Experience has shown that DIABINESE can replace insulin even in patients whose requirements exceed 40 units of insulin daily.[1] In other moderate to severe cases, adjunctive use of DIABINESE may improve 24-hour control while reducing the insulin requirement.[2]

1. Blöch, J., and Lenhardt, A.: Ann. New York Acad. Sc. 74:954, 1959.
2. A.M.A. Council on Drugs: J.A.M.A. 172:57, 1960.

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to replace or reduce insulin dosage

to ensure control where diet alone has failed

to realize the full potential of oral therapy

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ADMINISTRATION AND DOSAGE: Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Like insulin, DIABINESE dosage must be regulated to individual patient requirements. Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

SIDE EFFECTS: In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, DIABINESE should be discontinued.

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Reference: 1. Bunim, J. J., in Hollander, J. L.: Arthritis and Allied Conditions, ed. 6, Philadelphia, Lea & Febiger, 1960, p. 364.

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*Transatlantic Telephone Symposium, *The Effect of Estrogens in the Menopause*, Amsterdam/New York, 1959. Transcript available on request.





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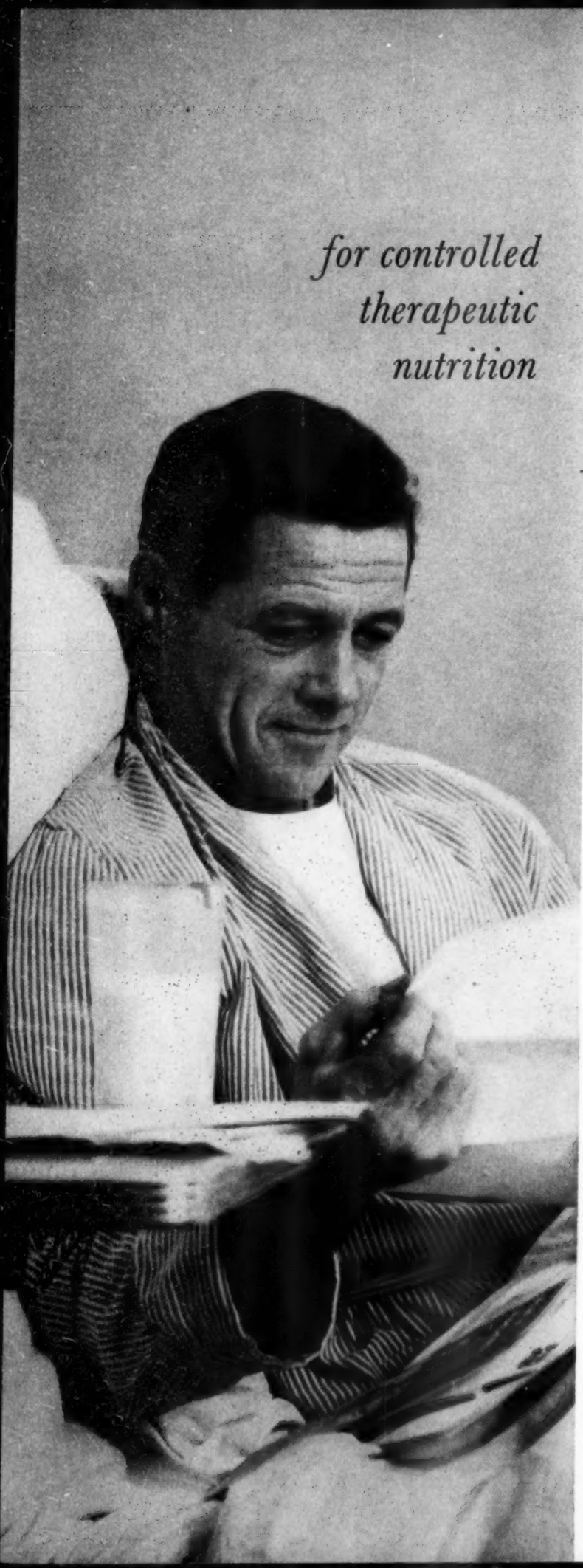
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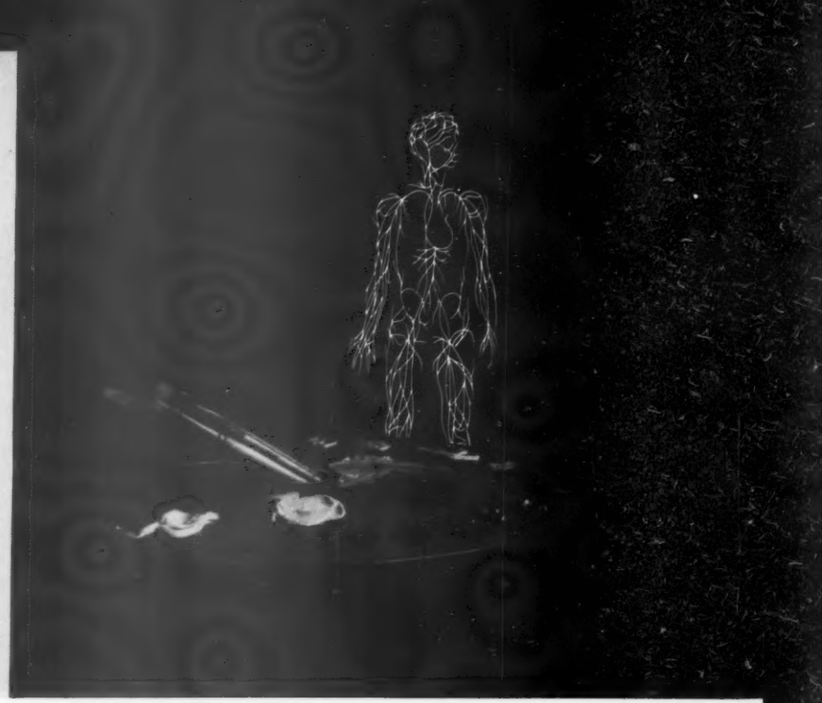
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1. Meilman, E.: Circulation 13:596, 1956

IN BRIEF

MODERIL is rescinnamine, a purified rauwolfia alkaloid useful in the gradual sustained lowering of blood pressure in mild to moderate labile hypertension. When MODERIL is given with other antihypertensive agents, the latter may often be administered in lower dosage with fewer undesired reactions.

INDICATIONS: Primary therapy in mild to moderate labile hypertension. In more severe cases, as adjunctive therapy with other agents.

ADMINISTRATION AND DOSAGE: Adjust dosage to minimum level for optimal therapeutic effect. Recommended initial dose—one 0.5 mg. tablet twice a day for two weeks. Significant side effects are unusual with MODERIL, but should they occur, reduce dosage to one 0.25 mg. tablet twice daily. When optimal hypotensive effects are obtained during initial period, this same reduced dosage or less may be used. If greater hypotensive effects than those observed during this period are required, cautiously increase dose by 0.25 mg. per day (up to 2.0 mg. per day) and consider combined therapy. Doses should be taken after meals to minimize possible adverse effects of increased gastric secretion.

Initial dosage for children 3-12 years of age is up to 0.25 mg. twice daily for one week. Children should be observed closely and when therapeutic effect is achieved, this dose should be reduced by half, i.e., 0.25 mg. daily.

SIDE EFFECTS: Same type as with reserpine but usually with reduced incidence or severity, e.g., mental depression, bradycardia, nightmares, and fatigue. Nasal stuffiness or congestion may occur but usually disappears with discontinuation of the drug or on use of topical vasoconstrictors or antihistamines. Increased frequency of defecation and/or looseness of stools is an occasional reaction. There have been occasional reports of serious hypotension in persons on rauwolfia compounds who undergo surgery with general or spinal anesthesia. It is suggested that MODERIL be discontinued two weeks before surgery, when feasible, or other appropriate measures be taken.

PRECAUTIONS: Because rauwolfia preparations may increase gastric secretion, MODERIL should be used with caution in patients with a history of peptic ulcer.

SUPPLIED: Yellow, scored, oval tablets of 0.25 mg., bottles of 100 and 500; salmon, scored, oval tablets of 0.5 mg., bottles of 100.

More detailed professional information available on request.

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PFIZER LABORATORIES
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Protects the angina patient better than vasodilators alone

Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, can delay recovery.

This is why Miltrate gives better protection for the heart than vasodilators alone in coronary insufficiency, angina pectoris and postmyocardial infarction.

Miltrate contains PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. . . .

What is more important—Miltrate provides Miltown, a tranquilizer which, unlike phenobarbital, relieves tension in the apprehensive angina patient without inducing daytime fogginess.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition; his operative arteries are dilated to enhance myocardial blood supply—and he can carry on normal activities more effectively since his mental acuity is unimpaired by barbiturates.

REFERENCES: **1.** Ellis, L. B. *et al.:* Circulation *17*:945, May 1958. **2.** Friedlander, H. S.: Am. J. Cardiol. *1*:395, Mar. 1958. **3.** Riseman, J.E.F.: New England J. Med. *261*:1017, Nov. 12, 1959. **4.** Russek, H. I. *et al.:* Circulation *12*:169, Aug. 1955. **5.** Russek, H. I.: Am. J. Cardiol. *3*:547, April 1959. **6.** Tortora, A. R.: Delaware M. J. *30*:298, Oct. 1958. **7.** Waldman, S. and Peiner, L.: Am. Pract. & Digest Treat. *8*:1075, July 1957.

Supplied: Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

Dosage: 1 or 2 tablets q.i.d. *before meals* and at bedtime, according to individual requirements.

CML-3619

Miltrate®

Miltown® (meprobamate) + PETN

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GENTLE STIMULATION OF COLONIC PERISTALSIS

without whipping the bowel

The active principle of Dorbane reaches the colon through the circulation. It acts directly and selectively upon the intrinsic plexus of the colon. The small bowel is not affected. Within 6 to 12 hours evacuation occurs without cramping or griping. Nonhabituating. Each scored tablet of Dorbane contains 75 mg., and each teaspoonful of orange-flavored liquid contains 37.5 mg. of 1,8 dihydroxyanthraquinone. Suitable for patients of all ages.

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Dorbantyl Forte offers double strength dosage of the Dorbantyl combination for greater convenience and economy for patients requiring extra potency. In orange-and-gray capsules.

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Northridge, California

Not all, but almost all allergic patients respond to the basic antihistamine Pyribenzamine®

Among these 5 cases, for example...



Miss J. W. responds to Pyribenzamine

Miss W. has had hay fever for 20 years. Condition is most severe in August. One Pyribenzamine Tablet t.i.d. during allergic episodes brings marked improvement — no side effects.



Mr. D. L. responds to Pyribenzamine

Symptoms of seasonal allergic rhinitis persisted in Mr. L. despite treatment with an antihistamine-decongestant spray and an oral antihistamine. Desensitization brought only moderate relief. On one Pyribenzamine Lontab b.i.d., Mr. L. did very well and was completely comfortable.



Mrs. E. E. responds to Pyribenzamine

When Mrs. E.'s allergic rhinitis failed to respond to other long-acting antihistamines, her physician prescribed Pyribenzamine Lontabs. Result: Sneezing, tearing and nasal congestion "just about disappeared."



Miss T. E. does not respond to Pyribenzamine

Miss E. has allergic symptoms (itching of eyes, skin irritation, nasal congestion) throughout the year with hay fever in August and September. Physician reports Pyribenzamine not effective; patient now takes diphenhydramine hydrochloride.



Mrs. B. R. responds to Pyribenzamine

Rose fever and hay fever plagued Mrs. R. Her physician reports therapy with Pyribenzamine "extremely successful." Mrs. R. states that after taking the drug "everything is fine in about 20 minutes."

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